

A Broader Debate on Energy

WITH the sudden attention that energy and its wise use is receiving world-wide, it was appropriate that the Royal Society should have convened a meeting to discuss 'Energy in the 1980s' last week. By an amusing coincidence, it started on the day the advertising signs were extinguished in Piccadilly Circus. There was more to our interest in the meeting, however, than simply the (fulfilled) expectation of adding to our knowledge in the field. If scientists and technologists are to speak to the public beyond their own community in a manner that will stimulate discussion and understanding, form is every bit as important as content, so we were particularly interested in the shape that the meeting would take. Two weeks ago *Nature* reported unfavourably on an energy meeting convened by the Royal Society of Canada (246, 56; 1973) largely on the grounds of its conventional format; could this one produce something new?

That it did not was no discredit to Sir Peter Kent who had assembled a distinguished list of speakers. Relevance, however, increases greatly with the proximity of the threat, and since the meeting had been announced, the question had changed dramatically from being what will we have in the 1980s to what will we make do with in 1974. One by one specialists discussed dispassionately their particular interests and supplied a multitude of data but the projections into the 1980s were cautious and assumed a relatively undisturbed society and no surprises, pleasant or otherwise. What was needed to complement these strands was a shuttle to weave cross threads and put the story together according to different patterns. What happens to the projections when oil supplies are cut by 10% in 1973? If the nuclear programme falters how are the other resources strained? If several as yet underdeveloped countries with large populations suddenly acquired an appetite for energy how would projections be affected? (We are, after all, at present seeing the consequences in the world food situation of the growing appetites of developing countries for protein.) And perhaps the key question—is energy saving, either voluntary or compulsory, going to make any impact on energy needs? It may be that what meetings of this sort need is the stimulus of a longish paper which has been read by everyone previously and which is sufficiently provocative that experts can spend their time dismembering and rebuilding rather than pursuing independent paths. Certainly some sort of interlocutor would be a useful addition.

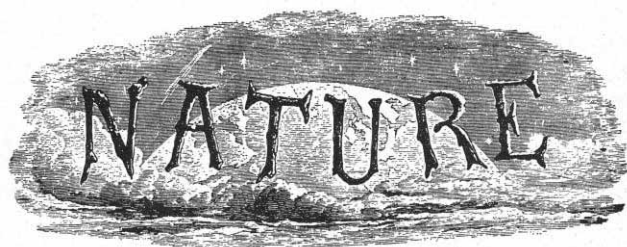
As it happened, the lack of a feel for total situations at the meeting was balanced by the simultaneous launching (surely no accident) of a document by the Friends of the Earth. This booklet, 'World Energy Strategies' by Amory Lovins, is worth reading if only because the author does attempt a synthesis. He works from the hypothesis that a "resource inventory would by itself be useless . . . energy constraints are not mainly dictated by physical scarcity, but are geopolitical, environmental and socio-technical".

Mr Lovins sees coal as the short and medium term solution to the energy problem. On the way to this conclusion, he comes up with some fairly predictable views

on the need for constraint in energy usage, particularly in the United States, some caustic words on the safety risks of nuclear fission and some hopeful thoughts on coal. He concludes that "the problems of coal are substantial but can be solved" whereas "governments should suspend their nuclear programmes until enough infallible people can be found to operate them for the next few hundred thousand years". This is an outspoken and biased point of view. Mr Lovins is prepared to give coal the benefit of every doubt, nuclear energy the benefit of none. Nuclear energy has to be judged not only by technical standards but by ethical considerations, whereas coal, the pursuit of which mars thousands annually but which lacks the magical ability to afflict unborn generations, is let off the social hook with a naïve reference to a recently opened Illinois deep mine which "is said to use every kind of safety and health precaution yet still is profitable." We are not the first to point Mr Lovins to Otto Frisch's delightful essay 'On the feasibility of coal-driven power stations'.

Nonetheless, Mr Lovins is a great asset and should not be lightly dismissed. For too long, discussion of broad multidisciplinary issues in the United Kingdom has been subordinated to the pursuit of excellence in individual fields. Decision making has been regarded as so much a province of government that national discussions of policy issues have been sadly lacking. For all that we may disagree with the Mr Lovinses, we need them in order to open up the debate. Preferably we need them on the same platforms as the experts and certainly we need them to make a nuisance of themselves.

100 Years Ago



A HEALTHY HOUSE

What a House should be, versus Death in the House. By William Bardwell, Architect and Sanitary Engineer, (London: Dean and Son.)

It would be interesting to have had some references given to sanction our author in claiming the authority of the Duke of Wellington, together with that of Aaron and the High Priests, his successors, for the practice of placing their beds nearly north and south so as to be in the line of the magnetic current. The theory no doubt has its advocates, but can hardly be of universal application, as there are many sound sleepers at all degrees of orientation.

From *Nature*, 9, 60, 61, November 27, 1873.



NEWS

More Uranium Found in Britain

THE Institute of Geological Studies reported this week that uranium is to be found in North Wales, the Southern Pennines, the South Wales coalfield, the Midlands as well as in the north of Scotland and south west England. (*Uranium Mineralisation*. . . , S. H. U. Bowie, D. Ostle and C. B. Campbell, IMM Applied Earth Science Transactions Section B, November 1973.)

Deposits in Scotland and in south west England have been previously reported by the IGS. A few thousand tons of uranium in the oxide form, U_3O_8 , are to be found in Caithness and Orkney and a few hundreds of tons in the south west of England.

The extent of the deposits now found in Wales and other parts of England are not revealed but the strength, in terms of parts per million of uranium ore, makes it clear that the deposits are at present not of economic significance. But they represent reserves, which if they turn out to be of sufficient tonnage, might well prove to be of strategic importance. The possibility of mining these deposits will not arise until the high quality ore at present being mined in Canada and South Africa are worked out and the cost of ore inexorably rises.

The deposits in the Orkneys are low grade and widespread but Dr Bowie and colleagues report that in places the content of uranium in phosphatic rock is as high as 1,000 parts per million, amounting to 0.1% enrichment, which compares favourably with the quality of uranium ore now being mined in other parts of the world. But the uranium content of the dark shales in the Orkneys rarely exceeds 200 parts per million. In the south west of England, however, the ore is found in high grade concentrations but of low tonnage. The new survey revealed, however, several new sources of uranium but they are also of modest tonnage or low grades. At Fingle Bridge, a rich zone has been found of 0.5% enrichment which is over 5 feet wide.

At Lutton on the western side of Dartmoor a vein has been found which is one foot wide, and a sample analysis showed that the uranium content was of the order of 3%. This same vein contains also copper, lead, silver and arsenic.

Several other sources of uranium have been found in the south west of England but the full extent of some of the deposits can not be revealed unless drilling takes place.

The present survey was restricted to sampling of stream water, sediment, wells and boreholes. When the terrain was suitable the countryside was scanned for evidence of radioactivity by carrying scintillation counters in vehicles and in some place by scanning for radioactivity on foot.

Of the newly reported finds of uranium, the IGS team reports that although some uranium is to be found in North Wales, it is not of economic grade. "The rocks represent a major crystal enrichment but no evidence has yet been found of uranium concentrations sufficient to produce deposits of potential value."

The uranium concentrations in the southern Pennines are very low (10–30 parts per million) but in the South Wales coalfield, concentrations of 270 ppm have been found. It is unlikely, however, that the element is present here in sufficient quantities to be of economic significance, according to Dr Bowie and colleagues. The highest concentration

of uranium found in the Midlands amounted to 162 ppm and this is in a shallow peat deposit.

No marked radioactivity was found in extensive examinations across the Midlands, from the Welsh borderland in Montgomeryshire and Radnorshire to Lincolnshire and Nottinghamshire except for some activity near the known outcrop of Cambrian shale near Nuneaton.

Uranium has never been mined on a large scale in Britain although it was obtained as a by product of a pitch blend mine near St Austell earlier this century. Britain, however, is not likely ever to produce enough uranium to fulfill its needs. The nuclear reactors at present in operation in Britain need more than a thousand tons of uranium a year to keep them in production. When it does become economic to think of mining uranium in Britain then the reported reserves (a few thousand tons of U_3O_8) represent at the present rate of usage, a few years' supply.

STEEL

European Opportunities

An improved coordination of steel research within Europe was called for by Dr Robert S. Barnes, director of research and development at the British Steel Corporation, last week. Dr Barnes, delivering the annual Hatfield memorial lecture, said that "the need to exchange technical views, to criticise, construct and develop cooperatively concepts for joint European research activity is now more necessary than ever it was".

Dr Barnes was critical of the arrangements existing at present within Europe for collaborative research in steel. The task of processing and assessing the waves of uncoordinated and untranslated proposals which sweep through the EEC and its advisory committees several times a year is too great, according to Dr Barnes. "The commission's advisory committees—there must be about a hundred of these—only deal with narrow technical areas and are often more concerned with technical details rather than with the broad needs for the individual research projects or with the eventual application of their outcome."

There is therefore a need for efforts to be concentrated on a few clearly defined and large projects, which for one

thing would ease the communication and administrative problems of steel research in Europe, said Dr Barnes.

In order to achieve these objectives, the European Commission will have to be advised in a different way. At present the commission's advisory experts are appointed as individuals and it would be advantageous if these experts represented the collective view of the European steel industry. Dr Barnes called for the industry to set up just such an organisation which would "produce and regularly update a strategy for collaborative research". It is possible that l'Association Européenne pour la Promotion de la Recherche Technique en Siderurgie could fill this role.

Dr Barnes also highlighted in his lecture a possible way of making steel in the future by using the gas emitted from a High Temperature Nuclear Reactor as a reducing agent. The gas would first be used to convert the iron ore to a pre-reduced iron. This would then be fed to an electric arc powered by electricity obtained from the waste heat of the first process.

Such direct use of nuclear power could be the way in which most steel will be made in the twenty-first century. It could, however, be introduced even sooner if the costs of using other forms of energy, such as coal or electricity, escalate faster than anticipated.

NUCLEAR REACTORS

Britain's Power Dilemma

THE miners, Arabs and power workers between them made life so bad for Britain's power industries last week that a meeting of the Nuclear Power Advisory Board, which was to take another step along the troubled road to choosing Britain's next reactor type, had to be cancelled. Everyone had too much on their plates already.

An announcement is expected early next year from Mr Peter Walker, Secretary of State for Trade and Industry, on which type of reactor Britain is to build next.

The Nuclear Power Advisory Board has already had presentations from the chief parties interested in the choice and has learnt from the Central Electricity Generating Board that it wants to buy light water reactors from the United States—preferably Pressurized Water Reactors (PWRs) from Westinghouse.

The board argues that the light water reactors are cheaper and more proven than anything else available. The alternatives are fourfold. Britain could build more Advanced Gas Cooled Reactors. Five of these are being built. All of them are late, and the first is not due to produce full power until 1975.

Two of the other possibilities require development. These are the Steam Generating Heavy Water Reactor, a 100 MW prototype of which has been performing well at Winfrith in Dorset since 1967, and the High Temperature Reactor. But the board argues that it is too late to build SGHWR. It offers too little export or development potential, is more expensive than the PWR, a development programme would be required with all its attendant risks and substantial quantities of heavy water would be needed. The High Temperature Reactor also suffers from the need for a development programme. A 30 MW prototype has been operating since 1963, but 30 MW is a far cry from the 1,200 MW size that interests the CEBG. The board is relatively enthusiastic about the design, however, and would like to see a commercial plant built. But it does not want to use the HTR for the large scale programme it is envisaging—six to eight stations on order by 1980. It would rather see the design developed more slowly.

The final possibility is that another Magnox station could be built. In spite of corrosion problems, Magnox stations have performed well and last year produced some of the cheapest electricity. With some redesign work to remove corrosion problems more Magnox stations could be a reliable bet. But the board believes the cost to be prohibitive, perhaps £600 million a station as against about £400 million for a more modern design.

The argument is not quite as simple as the CEBG would have everyone believe. For a start it is unfortunate, to say the least, that the empty order books of the nuclear industry, the government's commitment to reach a decision soon and the CEBG's belief that it will need more nuclear stations by the end of the decade have all combined to force a decision now rather than in eighteen months or two years time, when it will be seen whether at least one of the Advanced Gas Cooled Reactors, costing between them rather more than £1,000 million, works. Equally the CEBG's calculations studiously ignore the question of foreign exchange. With a trade gap running at £289 million in a single month, the government cannot be eager to spend more money abroad than it has to. And a first PWR would be bought lock and stock, if not barrel, from the United States. As the CEBG sees it, Britain's GEC-dominated National Nuclear Corporation would provide the emergency core cooling system, the containment and the chemical engineering of the new station, but the remainder of the nuclear steam supply system would come from abroad.

And the question of safety remains to be answered. The United States Atomic Energy Commission has spent the past two years arguing in public and private about the effectiveness of the Emergency Core Cooling System (ECCS) that is a key part of the PWRs' defence system against a bad nuclear accident. Theoretically the ECCS douses the reactor core in water within seconds of, for example, a broken pipe or blocked pump cutting off the normal cooling water supply to the core. Without water, a dry core heats to 1,800° C within a minute, at which point the fuel and zirconium fuel cans begin to melt. An hour after the loss of cooling water the core has flowed to the bottom of the reactor vessel accompanied by steam explosions which, combined with gas pressure, could split the reactor vessel, releasing fission products. A few hours after that, the molten core would have eaten through the reactor vessel and the concrete foundations.

The ECCS is designed to prevent this happening. But no practical test of the system has been made, and an AEC facility known as the Loss of Fluid Test Facility will not be ready to run the crucial experiments on what does actually happen to a dry core until 1975. Theoretical calculations suggested that the emergency core cooling system would prevent these events. But other sums produced different answers, and a small scale test on a simulated reactor core suggested that in the event of 30 to 100% of the cooling water leaving the reactor, only 10% of the emergency cooling water would reach the core. The Loss of Fluid Test should confirm

or quell these doubts. But the answers will not be available by January when Mr Walker has to make his decision.

The CEBG is of course aware of these problems. It has looked at the calculations at its nuclear laboratories at Cheltenham and concluded that the light water reactors are safe enough. But its conclusion is not going unchallenged. The Friends of the Earth have just launched a campaign on energy and its conservation. Their sister organisation in the United States has been at the forefront of the campaign against light water reactors. Last week a spokesman for the British end of the organisation said that "it is a little difficult to explain" how the CEBG has managed to satisfy itself about the safety of light water reactors while the Atomic Energy Commission is still sorting out the problem.

Aside from the safety matter, it is not at all certain that building PWRs will be as easy as the board maintains. Its interest lies in 2,400 MW stations consisting of two 1,200 MW sets. The largest PWR built and operating to date is 1,050 MW. And in spite of talk about buying proven designs, no reactor comes off the shelf. British industry will have to learn to build PWRs just as it has had to learn to build AGRs or would have to learn to build commercial HTRs or SGHWRs. Walt Patterson, a nuclear physicist who works with Friends of the Earth, says "the whole AGR fiasco is entirely conceivable as a re-run with light water reactors". Additionally the complaint is common within the industry and the United Kingdom Atomic Energy Authority that the CEBG cannot resist fiddling with power station designs.

A final question worth asking is why the government, the Atomic Energy Authority, the generating boards and the industry have the current problem to solve at all.

The CEBG seems happy to consign the AGR to oblivion. Yet it is the

Forthcoming Natures

NEXT week, *Nature* will contain a thirty-two page supplement reviewing science in Australasia.

Nature for Friday, December 14, will be a Christmas issue. In addition to the regular features there will be several pages of specially commissioned articles, chess problems and a quiz.

The two Friday issues of December 21 and 28 will be combined in one large edition that will be published December 21. *Nature Physical Science* and *Nature New Biology* will likewise be published in double issues on December 17 and December 19 respectively.

board that ordered the reactor in the first place, commissioned three separate designs and agreed to build these before a full prototype was constructed. (The Windscale AGR, well though it has run, is a far simpler machine than the commercial stations, built more for fuel testing than as a proper prototype.) The stations were all approved without detailed design work being undertaken.

It is a similar mess that everyone is trying to avoid this time. The choice is not an easy one. As Sir John Hill, Chairman of the Atomic Energy Authority, said at the Royal Society symposium on energy last week "all reactor systems have some problems". He also pointed out that "every time there is a major change of design there will be difficulties". It is possible that light water reactors will prove the final choice. But the CEGB should admit that the case is not as clear cut as it claims.

AUTOMOBILE POLLUTION

GM Breaks Ranks

by our Washington Correspondent
MOTOR manufacturers have recently failed in a last ditch attempt to keep exhaust catalysts off cars sold next year. For months, executives from the car industry have been badgering Congressmen and Senators, trying to win yet another delay in implementing the stringent exhaust emission controls specified by the Clean Air Act, and the matter finally came to a head early this month when the Senate Public Works Committee held a couple of days of hearings on automobile pollution. Spokesmen for the industry warmed over a number of old arguments, seized upon all kinds of real or imaginary fears, and invoked threats of economic and social disaster if the Clean Air Act is not soon modified. But the chief outcome seems to be a huge split in their own ranks.

They were arguing, essentially, for emission controls to be frozen at their present levels for the next two years, and for some rather more stringent controls to be imposed in 1977. Such a delay would put off the need to fit exhaust catalysts, since the present regulations can be met with engine modifications, and the clear intention is to use the breathing space to work to put off that fateful day entirely.

That, at least, is the position taken by representatives of Ford and Chrysler, who were unstinting in their criticisms of the catalyst. But witnesses from the other member of the big three, General Motors, broke ranks and came out with some extraordinary statements in support of the device. But they, too, want the controls relaxed, although only by a small amount.

In any case, Russell Train, Admini-

strator of the Environmental Protection Agency, said that he is not prepared to recommend relaxing or delaying the standards, and the committee shows no sign of taking the initiative itself. Thus, as John J. Riccardo, president of Chrysler put it, since "action must be taken now, or it will be too late", exhaust catalysts will be fitted to cars sold next year.

It was a last ditch attempt by Ford and Chrysler because the Environmental Protection Agency has already given them the maximum amount of time available to meet the standards, and the only possible way to delay things further would be for Congress to modify the Clean Air Act. The act requires that 1975 model cars emit 90% less carbon monoxide and oxides of nitrogen than 1970 models, and that 1976 models emit 90% less oxides of nitrogen than 1971 models. Earlier this year, however, the motor manufacturers persuaded the Environmental Protection Agency to give them an extra year to meet the standards. But part of the EPA's bargain included a provision which requires that all 1975 model cars sold in California must meet strict emission controls—and that will need the use of exhaust catalysts on those cars. The rationale was to force catalysts to be introduced in California next year—1975 model cars will be unveiled in the Autumn of 1974—and nationwide a year later.

Ford and Chrysler executives argued, as they have done for the past two years, that the catalyst is inherently bad technology, and that they would like to use better devices, such as the stratified charge engine, if only they had the time to do it. But, if they are forced to clean up car emissions immediately, they have no alternative to sinking their money into exhaust catalysts at the expense of developing the other technologies.

Six months ago, that was also the complaint put out by General Motors, but at the hearings earlier this month, Edward N. Cole, the company's president, said bluntly that there is no need to modify the interim regulations set for California in 1975, and that the conventional engine equipped with catalytic converters will be the best method of cleaning up automobile pollution. Cole also said that GM cars will be able to meet the 1975 interim standards, and that catalysts will be fitted not only to cars sold in California, but to others as well.

The effect of the split in Detroit's previously united front had the effect of undermining many of the arguments put up for delaying the standards, and environmentalist witnesses at the hearings had little difficulty in playing off one statement from the car manufacturers against another. But it is

perhaps worth noting, in any case, that only a few months ago, when spokesmen for all three manufacturers were arguing for a year's delay in the 1975 standards, that they all painted pictures of economic disruption and wholesale closures if they were forced to introduce catalysts on all their cars next year. Now, however, not only is General Motors planning to introduce catalysts nationwide next year, but Ford is also planning to fit them to all their California cars and 65% of their others. Environmentalists have been quick to ask what happened to the dire forecasts.

As for the latest round in the battle, the arguments for delaying the standards have revolved around three chief questions—are the standards stricter than necessary simply to protect public health? Will the catalysts lead to another serious health problem, namely, the production of sulphuric acid from sulphur in petrol? And, finally, will they contribute to the energy crisis by decreasing engine efficiency? In each case, Ford and Chrysler argued that it would be sensible to delay implementing the standards until those questions have been answered. Clearly, if catalysts are installed next year and it subsequently turns out that they are not needed, several hundred million dollars will have been wasted.

The question of the standards being stricter than necessary is one on which the manufacturers are almost united, and they have also received direct and indirect support from the National Academy of Sciences for their arguments. In September, for example, Dr Arthur Stern, chairman of an NAS committee which has been looking into auto pollution, said that he believes the standards are three times stricter than necessary. That statement has, of course, been seized by the manufacturers and bandied about in committee rooms and Congressmen's offices ever since, but they are looking to the academy to provide even more support for their case next year. The academy has been given a contract by the Senate Public Works Committee to conduct a massive study of the health effects of pollutants, and the car manufacturers are convinced that when it reports next year, the academy will vindicate their own findings that the standards are much too strict.

In any case, the manufacturers have been arguing with some conviction that the 1975 interim standards should be delayed until the academy has produced its report, since, by next summer, catalysts will already be clamped to car exhausts and it will be too late to turn back if the study finds that they are not in fact needed. But the EPA, in the person of Mr Train, testified that relaxation of automobile controls next year would not only take the steam out of the

motor manufacturers efforts to clean up their products, but it would also cause many state governments grave problems in meeting other standards specified by the clean air act. He thus refused to entertain the idea of yet another delay.

As for the question of sulphuric acid emissions, that has already caused a split within the Environmental Protection Agency and raised some genuine fears that the catalyst may cause almost as many problems as it solves. The problem is the catalytic converters oxidise not only carbon monoxide and hydrocarbons to carbon dioxide and water, but they also oxidise some of the sulphur in gasoline to sulphur trioxide, and that could result in dangerous levels of sulphuric acid and sulphates in city air.

The problem first came to light earlier this year, and it prompted the EPA's director of research and development to suggest in an internal memorandum that the introduction of catalysts should be delayed until the problem has been given further study. According to the EPA's latest estimates, cars equipped with catalysts will spew between 3 and 5 times more sulphate into the atmosphere than cars not equipped with converters. Mr Train also stated at the hearings that EPA scientists have concluded that unless a mechanism is developed to control sulphate emissions, "more than one model year of cars equipped with catalysts could result in ambient levels of sulphates reaching levels at which recent studies suggest there will be adverse health effects". The EPA will soon be releasing a technical report on the matter, but in any case Train emphasises that if a problem does arise, there will be ample time to find a solution before there is a public health risk. Moreover, Mr Cole testified that "our (GM's) tests and atmospheric modelling show that while there may be some possibility, there is little probability that roadside atmospheric levels of sulphates from catalyst equipped vehicles by themselves will reach any threshold health levels".

But it is on the question of petrol consumption that General Motors testimony was most seriously out of line with that of the other two motor manufacturers. Until recently, all three car makers have been arguing that the exhaust catalyst will greatly increase fuel consumption, a fact that will not do much to help solve the energy crisis. But, much to the dismay of Ford and Chrysler, Mr Cole told the Senate committee that General Motors' cars equipped with catalysts to meet the 1975 emission standards will consume on average 13% less fuel than models being sold this year. To be sure, part of the reason for the dramatic drop is explained by the fact that GM, along with other manufacturers, will be pro-

ducing smaller cars, but the statement has clearly cut the ground from under Ford and Chrysler's attempts to ride the energy crisis bandwagon to put public opinion on their side in the battle against the catalyst.

Thus it seems inevitable that catalysts will be fitted to some 60% of all cars sold in the United States next year. But the debate will carry on for years to come.

ROYAL SOCIETY

Future Energy Sources

ENERGY in the 1980s, last week's symposium at the Royal Society, painted several different pictures of future trends. Mr D. Clark of the Central Electricity Generating Board, pointing out that his board is the largest consumer of fuel in Europe, stated that coal will be the board's staple fuel until the 1980s, when oil will become increasingly more important. The future after that will lie largely with nuclear power.

Up to the 1980s, Mr Clark said, the board can use all the coal that the National Coal Board can provide providing the price is right. But nuclear power will quickly become economical for lower load factors than at present. With forecasts based on a 5% growth rate, the year 2000 would see 24% of Britain's energy needs supplied by nuclear power. Towards the end of the 1980s, surplus nuclear generating capacity should be available on enough nights of the year to make energy storage a practicality.

But while coal still has a large part to play, Mr Clark was clearly not entirely happy at the prospect. "It is a fact", he said, "that over the last fifteen years electricity production has been hit a lot harder by stoppages in coal supplies than in oil supplies."

He also suggested that the volume of ordering of new coal-fired plant will be too small for technical innovations of any dramatic kind in coal plant.

Mr Leslie Grainger of the National Coal Board disagreed. By his calculations, the price of coal has virtually to double before nuclear power becomes competitive for low load generation. Advances in coal utilisation such as fluidised combustion, liquefaction and gasification were all put forward.

"The time has come", Mr Grainger said, "when we should increase the scale of this operation". A demonstration fluidised combustion plant should be built and a fluidised liquefaction plant producing 10 tons a day should be constructed (a half ton a day plant is already running). Coal is going to be very important on a world scale for many decades, Mr Grainger added, and will increasingly be used for conversion to other forms of energy.

Mr E. B. Walker of Gulf Oil Cor-

poration was also optimistic about energy conversion. His interests lay in converting tar sands, oil shales and coal. By 1985, he predicted, 3.75 million barrels of synthetic oil a day will be being produced in the USA. "This will reduce the United States demands on world supplies," he added, "and will therefore greatly strengthen the free world", although it is highly unlikely that any of the synthetics will be exported. Oil extracted with hot water from tar sands is already being produced at the rate of 50,000 barrels a day and Gulf plan to invest \$900 million in a plant that will produce more than twice that amount. Two tons of tar sand produce about one barrel of crude. About the same amount of shale also produce a barrel of oil. But production difficulties in the arid Rocky Mountains mean that there will be long lean times before this source produces large quantities of oil. The cost of these synthetic crudes lies between \$4 and \$7 a barrel at 1970 prices.

Sir Peter Kent, Chairman of the Natural Environment Research Council and a former exploration manager with British Petroleum, warned of the difficulties that have already occurred in bringing North Sea Oil ashore. Pipelines are being laid at twice the usual depth for offshore oil in a stormy stretch of sea and "delays may very well arise".

Happy Hundredth

SIR RICKARD CHRISTOPHERS is 100 next Tuesday, November 27.

He started his scientific career in 1898 as a member of the Malaria Commission, jointly appointed by the Royal Society and the Colonial Office. Ronald Ross had just published his classical work on the mosquito as vector and Christophers, with his deep understanding of insects, was able to exert an enormous influence on the study of diseases borne by mosquitoes. He worked largely in India until 1930 and then returned to London to continue at the London School of Hygiene and Tropical Medicine. On retirement in 1938, he moved to Cambridge and spent part of the war working on insect repellents. From his reports to the Malaria Committee (1900-02) to his 700-page volume '*Aedes aegypti*—the Yellow Fever Mosquito' (1960) his publications have been of the greatest distinction.

Sir Rickard finally moved to Dorset in 1963 where he spends much of his time gardening. A full tribute appears in *Trans. R. Soc. trop. Med. Hyg.*, 67, 729 (1973).

Short Notes

Population Dilemma

"We must reduce, halve and eventually reverse the present population growth rate." These were the words used in London on Wednesday by Mr Ron Dick, director of Population Countdown, at the start of the organisation's campaign for World Population Year.

Population Countdown aims to raise £150,000 during 1974—World Population Year. The money will be spent on supporting family planning projects throughout the world as well as on making the people of Britain aware of the world's growing population.

Between now and the end of the year Population Countdown will spend £12,000 on advertising in Britain. This money, Mr Dick said earlier this week, has come from a "special donor".

Less than 15% of the money collected by the organisation will go on overheads according to Mr Dick. The eventual aim of the campaign is to raise £1 million a year by 1977–78. During 1974 Mr Dick hopes to set up about 100 local groups throughout Britain to help with the appeal.

Population Countdown is a revamped version of an organisation set up by the Family Planning Association two years ago. In its old form the organisation was not too successful in raising money. But Mr Dick is confident that Population Countdown will meet its stated aims.

In the wake of the flood

THE *Financial Times* may have informed its readers in headline last week that the return of the horse is not the answer to Britain's energy crisis, but other organisations are not so bashful. The Inland Waterways Association has seized the chance of Arab oil embargoes to inform the government that its duty is to "consider methods of reducing our consumption of fuels without jeopardising our industrial viability. Transport, accounting for over one-fifth of our total energy consumption, offers the possibility of such economies". Quoting a 1972 report from Oak Ridge National Laboratory in the United States the association claims that waterways are four times more efficient than roads in terms of fuel consumption.

The Europeans are well aware of the advantages of water transport, the association says. "We ask that the Government, in the interest of fuel economy should update transport investment policy to include a realistic assessment of inland water transport on major new or enlarged waterways".

Less labour, less pollution, less noise,

less road congestion and lower freight rates are the advantages. Can the government refuse?

Indian-Soviet Collaboration

THE plans for launching an Indian research satellite by a Soviet rocket from a base within the Soviet Union are now past the first stage, according to Academician Boris N. Petrov, Chairman of the Interkosmos Council. The organisational basis for the joint project has been established, and the working plans completed. Now all that is necessary, it would seem, is for the satellite to be built.

According to Academician Petrov, "dynamic and static tests on a volume-weight mockup" of the satellite are now under way. The Soviets will provide the rocket—which will be similar to those used to launch the joint Comecon "Interkosmos" satellites. They are also assisting the Indian designers with certain auxiliary systems and elements for the satellite itself. According to the Indian director of the research team, the satellite is intended to monitor solar neutrons and gamma-rays, X-radiation of cosmic origin and also to investigate the ionosphere. Flight control and telemetry will be carried out from bases in both the Soviet Union and in India. The satellite is envisaged by the 200-strong Indian team as only the first step in an extensive space research programme, which will eventually cover applications to meteorology, communications, navigation and mineralogical surveying.

Law of the Sea

A FINAL date has been fixed for the full United Nations Law of the Sea conference that should resolve many questions about territorial waters, patrimonial seas, the law of the high sea, pollution matters and the freedom of oceanography. The conference will get under way on June 20, 1974, at Caracas in Venezuela and is due to last ten weeks. The venue has been changed from Santiago following the recent Chilean coup. The USSR, among other countries, was not prepared to go there.

Neanderthal Remains

EXCAVATIONS at the palaeolithic site of Belogorsk (Crimea) are yielding further Neanderthal remains. Last year, part of the skull of an 11–12 year old child was discovered; further excavations have now revealed a femur, a radius, several vertebrae, and hand and foot bones. Interviewed in *Pravda* (November 12, 1973), Professor Vsevolod P. Yakimov, Director of Moscow Univer-

sity's Institute of Anthropology, said that the new finds probably came from the same skeleton as the skull. On the basis of preliminary investigations at the Institute, he assigns the burial an age of some 50,000 years. Excavations at Belogorsk, which were begun in 1971 by the Academy of Sciences of the Ukrainian SSR, have also yielded mammoth, horse, fox and wolf bones, as well as flint implements.

Blessing Bessborough

THE Institution of Civil Engineers has decided that the Bessborough Report on the Research Associations is, by and large, a good one. The institution has sent its comments on the report to the government and particularly welcomes the proposal that a Board of Industrial Research and Development should be formed with a standing similar to the research councils.

The establishment of the board, the ICE says, would allow coordination over the wide areas of interest that the forty-odd research associations cover. Integration of this research with the research councils and the government research establishments should also be possible.

The institution does, however, sound several warning notes. Increased research and development in the construction field would produce benefits far greater than the extra cost while ocean engineering in particular needs support.

The institution is also eager—along with the Bessborough committee—that more contract research from industry should be placed with the research associations.

More Sandwiches

SANDWICH courses are to come under investigation by a working party set up by the Universities, Polytechnics and Industry Committee.

The setting up of this group has been precipitated by a feeling in industry and in the education world that the increase in training places is not keeping pace with the growth of sandwich course places in the further and higher education sectors.

The group will consider, in general terms, the value of the sandwich course scheme. It will also investigate the future development and expansion of courses, the concomitant need for increased provision of industrial training places, and finance and long term policy in this area.

Dr G. Tolley, Principal of Sheffield Polytechnic, will be the group's chairman.

NEWS AND VIEWS

Redshifts of Quasistellar Objects

THE physical nature of quasistellar objects is as puzzling now as it was 10 years ago when their large redshifts were discovered. Within 3 years of those first redshift determinations the difficulties encountered theoretically in explaining the observed radio and optical properties of the QSOs, if they were indeed at the enormous distances derived cosmologically, had been clearly laid out. Attempts were made to find alternative explanations for the redshifts, in terms of local objects exploding outward from our Galaxy at relativistic velocities, or collapsed objects whose radii had shrunk to near the Schwarzschild limit so that huge gravitational redshifts were present. But these theories were unsatisfactory either on energetic grounds or because of lack of a physically viable model of such an object near the limiting Schwarzschild radius.

A small minority of workers have maintained a sceptical attitude toward the hypothesis that the QSO redshifts are cosmological in origin, produced by the expansion of the Universe. These workers have mostly accepted that no viable alternative theory for the redshifts exists at present, and they have either pressed for additional observations along any lines that appeared promising for settling the controversy, or they have attempted to devise and carry out such observational programmes themselves, or they have made attempts toward devising alternative theories. But above all they have tried to persuade workers to keep an open mind on the question and, especially, not to ignore any data which pointed toward non-cosmological redshifts.

The large majority of astronomers, however, has adhered to the cosmological hypothesis, because this works well for normal galaxies, and because any alternative hypothesis would involve some radical new thinking.

Unfortunately, it has been very difficult to devise observational tests to give a conclusive answer, because most have had to be based mainly on statistical arguments, or on a painstaking and time-consuming search for luminous connections between objects of different redshifts. To collect enough data when time on large telescopes is in great demand is a real problem. The lack of precision in radio source positions has also led to a considerable amount of wasted telescope time.

It is therefore very interesting that astronomers seem at last to be within shooting distance of making some crucial tests. This has come about mainly because of the recent dramatic improvement in the accuracy of radio positions, so that errors are down to 2 arc s or better in some cases, through work at Molonglo, Cambridge, Malvern and Jodrell Bank, and other radio telescopes now starting precision work.

Two exciting pieces of optical work, made possible by these improved positions, are reported in this issue of *Nature*. The first concerns the discovery of a second double QSO with very discrepant redshifts (Wampler *et al.*, on page 203), a joint result by optical workers at Lick Observatory and Hazard on the radio side. The first pair of QSOs with discrepant redshifts, discovered some time ago by Stockton, were 35 arc s apart, but the new pair are at only 5 arc s separation. There is in

addition a faint extended object very near, and the radio source is double with one component coinciding with the brighter of the QSOs. Such a configuration is highly suggestive of physical connection. The authors conclude that "our observation of a close pair of QSOs with discordant redshifts is unlikely under the cosmological hypothesis" and "we believe that these observations add support to non-cosmological theories of redshifts". They also point out some interesting near-coincidences in wavelength: if the brighter and fainter QSOs are a and b , $(1+z)_b \approx 2(1+z)_a$; an absorption feature appears in b very near the wavelength at which strong MgII2800 emission occurs in a but it is probably the CIV1549 doublet at a lesser redshift than the emission-line redshift in b . Finally, there is an emission in a at the same wavelength as strong CIV emission in b . The authors conclude that these all represent "either an unfortunate coincidence or a profound mystery".

The second paper (Hazard *et al.*, on page 205) is joint work by radio and optical astronomers at Hale and Lick Observatories. With the improved radio positions, a search was made for close groupings of blue stellar objects coincident with a radio source and with three or more galaxies near the BSO. The important point is that it was not known during the search whether the BSOs were QSOs or, of course, what their redshifts were. Previous work in which QSOs had been found in close proximity to galaxies had been of two sorts. Burbidge *et al.* had found four (and later a fifth) 3C QSOs lying close to fairly bright galaxies of very different redshifts, a result which yielded high statistical significance, but this result concerned strong radio sources and bright galaxies.

Several other workers have looked for faint groups or clusters of galaxies near QSOs of small redshift. Since the QSO redshifts are known and selected in advance, and since galaxy groupings selected are in the right magnitude range to have redshifts of approximately the QSO value, the investigations, which yielded galaxy redshifts agreeing with the QSO redshifts, were of course clearly biased toward finding support for the cosmological redshift hypothesis, as Hazard *et al.* pointed out. Their investigation is unbiased, and the results are very interesting.

Of four sources selected for study, one was in fact the double QSO described earlier. But in all the other three cases, the fact that the BSO proved to be a QSO of large redshift, obviously much larger than those of the nearby galaxy groups as indicated by their magnitudes, is most intriguing.

The authors point out that no statistical conclusions can be drawn with so few samples, and conclude by leaving open the question of the nature of the redshifts. But one may at last hope for a resolution of the problem; because of the new accurate radio positions, optical observers can spend telescope time examining all BSOs near a radio source and even objects of neutral or reddish colour. In this reviewer's opinion, the case for non-cosmological redshifts is already strong. E. M. B.

From Cyclic AMP to Cyclic GMP

CYCLIC AMP (3',5'-adenosine monophosphate) is now biochemical folklore and occupies the same hallowed position as its precursor, ATP (adenosine triphosphate). After a humble birth only 16 years ago, as a curiosity in Sutherland's work on the regulation by adrenaline of hepatic glycogen metabolism, by 1965 it was hailed as an almost universal 'second messenger' for hormones. Since then there has been no major biochemical regulatory event which has not been thought to be mediated by means of cyclic AMP (more than 2,000 papers, a dozen books on cyclic AMP this year and one more serial publication—*Recent Advances in Cyclic Nucleotide Research*—to add to the librarian's shopping list). Even if some of the hypotheses on the role of cyclic AMP are still questionable, this cyclic nucleotide has opened up new areas of research—phosphokinases and protein phosphorylation, gene activation in bacterial adaptation, cellular aggregation and slime mould differentiation, to quote only a few. What has attracted little attention during these past 5 or 10 years of intense activity are regulatory events in which cyclic AMP seems to have no part to play. Quite recently, however, a more interesting story than was imagined only a couple of years ago is emerging and this is where cyclic GMP (3',5'-guanosine monophosphate) comes in.

Already in 1969 Sutherland's laboratory had shown that cyclic GMP compound is present in urine and tissues of a variety of animals (Hardman *et al.*, *J. biol. Chem.*, **244**, 6354; 1969). It is interesting that tissues with relatively small concentrations of cyclic AMP, such as brain, testis and lung, are rich in cyclic GMP. Because of cyclic AMP's initial association with hormone research, the first indications that something important still lay concealed also arose from investigations on hormones. One can arbitrarily classify hormones into two categories: (1) those that act by controlling cyclic AMP activity in their target tissues, such as adrenaline, glucagon and almost all pituitary and hypothalamic polypeptide hormones; and (2) those that do not, such as steroid hormones, thyroid hormones, insulin and plant hormones.

It is studies on this second class of hormones that have yielded one of the clues to the involvement of cyclic GMP in biological regulation as, for example, the recent observation that insulin leads to increased activity of cyclic GMP in adipose and liver cells (Illiano *et al.*, *Proc. natn. Acad. Sci. U.S.A.*, **70**, 2443; 1973). Different groups of workers have also demonstrated that cyclic GMP when added to isolated tissues and cells has profound metabolic effects which could not be produced with cyclic AMP. Of particular importance are the findings of Greengard's group who showed that in lobster muscle and neuroblastoma cells there exist two quite distinct protein kinases—one dependent on cyclic AMP and the other on cyclic GMP (Kuo and Greengard, *J. biol. Chem.*, **245**, 2493; 1970). These workers, who have considerably advanced knowledge of the role of cyclic nucleotides in neural function, were also able to show that the cerebellum was particularly rich in a guanyl cyclase activity (conversion of GTP to cyclic GMP) and most tissues examined so far have now been shown to contain this enzyme. Several properties of this enzyme, not least its weak association with membranes, seem to be different from those of the classical membrane-bound adenylyl cyclase system which is responsible for the formation of cyclic AMP from ATP

(Hardman and Sutherland, *J. biol. Chem.*, **244**, 6363; 1969).

As with progress in many other areas of biochemistry, the speed and accuracy with which a new concept can be tested often depend on how successfully analytical technology could be tailored to tackle new questions. This is true for cyclic GMP. The extremely small intracellular amounts of this nucleotide (10–100 fmol g⁻¹, or 10–50 times smaller than those of cyclic AMP) meant that, until recently, the assays were extremely laborious and often unreliable. The radioimmunoassay method (Steiner *et al.*, *Adv. Biochem. Psychopharmac.*, **3**, 89; 1970), now tried out in many laboratories, has, however, opened the way for eventually establishing cyclic GMP as an important intracellular mediator of metabolic and growth regulation, perhaps of the same importance as cyclic AMP.

Thus, thanks to a reliable assay for cyclic GMP, several interesting differences between the two cyclic nucleotides are now apparent. First, hormones like insulin, cholinergic (acetylcholine) or other agents (histamine) important in neural function, and lentil mitogens, all of which are known not to depend on cyclic AMP for their action, now seem to act by way of cyclic GMP. Second, it is becoming more and more apparent that there exist not only distinct cyclases, but also distinct phosphodiesterases and cyclic nucleotide binding proteins (or phosphokinases) which suggests that sites of synthesis, degradation and action are not the same for the two cyclic nucleotides. Perhaps of even greater interest is the suggestion that the high concentrations of one cyclic nucleotide prevent the formation, metabolism or action of the other. Evidence for this is not always firm or unanimously accepted; for example, the suggestion that cyclic GMP may cause a reduction of intracellular concentrations of cyclic AMP by activating the specific phosphodiesterase for cyclic AMP is disputed.

Whatever will be the more acceptable conclusion for the above particular phenomenon, Goldberg at the University of Minnesota has been fascinated by the mutual antagonism between the two cyclic nucleotides and has recently formulated an interesting hypothesis, in which he and his collaborators rationalise the diverse effects of these two key purine metabolites. In a review which is to appear in volume 3 of *Recent Advances in Cyclic Nucleotide Research*, Goldberg and his colleagues say that a signal such as a hormone or a neurotransmitter may exert 'monodirectional' control of generating either cyclic AMP or cyclic GMP, with each nucleotide having a separate stimulatory effect. It seems that all such 'monodirectional' systems (for example, the regulation of salivary gland secretion by parathyroid hormone) are for some reason calcium-dependent. Goldberg and his colleagues also offer a 'bi-directional' model of control embodied in the 'dualism' or Yin-Yang hypothesis, based on an analogy from the classical Chinese precept which states that for every point of stimulation (say, of a nerve, as in the practice of acupuncture) there is a corresponding point of inhibition or suppression. Thus in a bi-directional system, stimulation or inhibition of a process is achieved by a simultaneous drop in concentrations of cyclic AMP as those of cyclic GMP increase, and indeed this seems to be the case in a variety of systems that these workers have examined.

The dualism or Yin-Yang hypothesis is also supported

by observations that cyclic GMP promotes events in the cell that are antagonistic to those mediated by cyclic AMP. Conversely, artificially increasing the intracellular concentration of cyclic AMP, as with theophylline, led to an abolition of the response to cyclic GMP whether given exogenously or generated within the cell. These observations are not often easy to record because the changes in amounts of cyclic GMP are very low and transitory and because of a further variable, calcium, which is required for most cyclic GMP mediated effects. Nevertheless, in making these observations Goldberg and his associates have laid open for future experimentation many interesting regulatory systems. In a recent paper by Goldberg's group (Estensen *et al.*, *Nature*, **245**, 458; 1973) it is shown that movement of leukocytes, which is known to be inhibited by cyclic AMP, is markedly promoted by cyclic GMP. They propose that chemotactic agents like cytochalasin B, phorbol myristate acetate (PMA) or acetylcholine may act by potentiating the action or increasing the concentration of cyclic GMP. Furthermore, anybody dealing with such important phenomena as cell proliferation, viral transformation of cells, induction of immune response, action of nerve growth factor, in which cyclic AMP has an inhibitory effect, ought to examine a positive involvement of cyclic GMP.

It is, after all, not very long since interest in cyclic GMP has been gathering momentum so that many of the observations noted here still await rigorous confirmation. Among the more important issues that will soon have to be settled are:

- The location of guanyl cyclase. It is believed that adenylyl cyclase is situated within the close proximity of

the receptor for the hormone, or other biologically active agent, within the plasma membrane of animal cells. If guanyl cyclase turns out not to be a membrane enzyme, then it raises the interesting question of the nature of its association with the cellular receptor; particularly for molecules such as insulin which are currently thought to act from outside the cell.

- Mere changes in the intracellular concentration of cyclic GMP are not sufficient evidence of a primary regulatory role for this cyclic nucleotide. It is therefore urgent to identify cyclic GMP binding protein(s), and in this context the distinctness of protein kinases dependent on cyclic AMP and cyclic GMP offers a valuable clue. One has here only to consider how valuable the recognition of cyclic AMP binding protein has been to establish the role of cyclic AMP as a mediator of gene activation in *Escherichia coli* (Pastan and Perlman, *Adv. Cyclic Nucleotide Res.*, **1**, 11; 1972). There is also the subsidiary issue of clarifying the role taken by calcium in the action of cyclic GMP.

- The more general biological problem of key metabolites, or 'second messenger', a term first coined for cyclic AMP, that have to be generated for a regulatory agent to exert its action will have to be considered. Will it stop at cyclic GMP or will there be a flood of similar intermediate control elements? (At least the cyclic pyrimidine monophosphates seem to have been ruled out.)

Answers to all these questions may require some patience, but judging from the exponential rate at which publications are appearing, it will not be long before cyclic GMP is established as the second 'second messenger'.
J. R. T.

Immunopathology of Parasitic Infection

MOST parasites are capable of evoking immune responses in their hosts but these are seldom effective in eliminating the infection because parasites have evolved a number of ways of evading the immune response and its consequences. Some, like the African trypanosomes and malaria parasites, continually change their antigens and outwit the immune response in this way. Others, like the schistosomes, incorporate host material into their surfaces and thus become immunologically invisible. A major problem in many parasitic diseases is that not only is the immune response ineffective but it may also give rise to a variety of pathological conditions. The immune response may therefore be counterproductive. Glomerulonephritis is a serious consequence of both African sleeping sickness and malaria and is thought to be initiated by the deposition of antibody-antigen complexes in the kidneys. The localised immune responses evoked to deal with these complexes have no effective role in protection. The parasites continue to multiply elsewhere in the body and soluble antigens pass into the circulation to give rise to the antibody-antigen complexes in the glomeruli.

The problems brought about by an immune response which takes place away from the site of infection also occur in schistosomiasis. The adult worms live in mesenteric blood vessels and their numbers are controlled by an immune response which has been completely manipulated by the parasite. The worm takes up host antigens from the blood and incorporates them into its

surface. Sheathed in host antigens, the worm is immunologically invisible but continues to pass antigens into the blood stream to elicit an immune response which is effective only against new invading forms as they migrate through the skin and underlying tissues of the host. This kind of response should produce a well balanced host-parasite relationship and prevent overcrowding of the worms. Crofton (*Parasitology*, **62**, 179; 1971) has pointed out that helminth infections tend to be overdispersed and most hosts harbour relatively small and easily tolerated worm burdens. In such circumstances only the very heavily infected hosts would be expected to die and most would not be unduly inconvenienced by the infection.

Unfortunately there is a major complication in schistosome infections. The female worms release large numbers of eggs which enter the blood stream and lodge in the small blood vessels in a variety of tissues especially the spleen, lungs and liver where up to 10,000 per gram may be found. These eggs cause granulomas to form. The granulomas begin as reactions involving macrophages, lymphocytes and eosinophils and later become fibrous. The formation of granulomas eventually leads to liver obstruction and liver function failure and, in experimentally infected animals, the liver may reach double its normal size. The granulomas are obviously very important in the pathology of schistosomiasis.

For many years it was widely held that the granulomas were the result of a cellular response to irritation but it is now known that their origin is immunological. This

realisation has gradually emerged from a carefully directed research programme extending over 16 years by K. S. Warren of the Case Western Reserve School of Medicine and a number of collaborators. Warren has summarised the evidence that granuloma formation results from a delayed hypersensitivity reaction (*Trans. roy. Soc. Trop. Med. Hyg.*, **66**, 417; 1972) and has since extended these findings with the collaboration of D. L. Boros who originally joined him as a post-doctoral research worker. On page 224 of this issue they describe how they, and Pelley, have isolated granulomas *in vitro* and have extracted from antigen stimulated granulomas a substance that inhibits the migration of macrophages and which they identify as a lymphokine. In another paper Boros and Warren (*Immunology*, **24**, 511; 1973) describe how the intravenous injection of bentonite particles impregnated with the antigen elicits granuloma formation in the lungs of sensitised mice.

The antigen is a soluble substance released from the egg. After the egg is laid embryonation occurs and this is accompanied by the liberation of enzymes and soluble antigens (which may be enzymes). The egg acts as a focus for the granuloma. Macrophages enter the immediate vicinity of the egg and come under the influence of the lymphokine and are unable to move away. In most bacterial and fungal infections this kind of local reaction isolates the invading organisms which are then phagocytosed by the macrophages. In schistosomiasis, however, a granuloma 100 times the size of the egg is formed and this is gradually replaced by fibrous scar tissue. Boros and Warren have also found that bentonite particles impregnated with mycobacterial and histoplasma antigens induce granulomas in animals sensitised with homologous antigens but not heterologous ones.

It is clear from these experiments that the pathology of schistosomiasis is not unique and comparable situations probably exist in a number of parasitic infections. The existence of non-protective delayed hypersensitivity states in parasitic diseases makes vaccination attempts potentially dangerous procedures which might even lead to immunological enhancement. The World Health Organisation (*Tech. Rep. Ser.*, No. 519, *Cell Mediated Immunity and Resistance to Infection*; 1973) is fully aware of this problem and as more information about

immunity to parasitic diseases accumulates the possibilities of developing useful methods of immunisation fade further and further into the distance.
F. E. G. C.

CONTRACEPTION

How Safe is Safe?

from a Correspondent

How safe is the 'safe' period as a means of contraception? This will depend among other things upon how long the ovum and sperm can exist in the reproductive tract without loss of the ability for fertilisation and how fixed in the menstrual cycle is the time of ovulation. Can ovulation in normally menstruating women occur at times other than at about mid-cycle? Can it be induced, or can spontaneous ovulation be hastened, by coitus? Although coitus-induced ovulation occurs in many species it is not usually considered to be a phenomenon in humans.

Jöchle (*Contraception*, **7**, 523; 1973) has now reviewed the evidence relating to this question. The length of the luteal phase of the cycle seems to be fairly fixed at about 14 days; variations

in menstrual cycle length usually result therefore from variability of the follicular phase. It is known that hypothalamic-pituitary-ovarian function can be modified by environmental change resulting in inhibition of ovulation and a consequent change of menstrual pattern or the complete absence of menstruation (psychogenic amenorrhoea).

The possibility exists therefore that other environmental changes might stimulate pituitary gonadotrophin secretion and produce ovulation. That ovulation can occur at times other than mid-cycle has been suggested by examination at autopsy of ovaries and uterus and calculation of the time interval in which ovulation must have occurred. When this interval was related to the time of menstruation of the previous cycle the results suggested that ovulation could occur at any time in the cycle. Similar observations made at surgical operations also suggested that ovulation could occur on any day of the first half of the cycle.

Evidence in support of coitus-induced ovulation was obtained from two sources. (1) Conceptions resulting from rape, using data only from patients for whom reliable information could be

Haemin Selectively Stimulates α Globin Synthesis

THE study of the role of haemin in protein synthesis is interesting because it provides evidence that some regulation takes place at the level of translation. When haemin is added to a cell-free system containing globin messenger RNA globin synthesis is stimulated, but so too is the synthesis of endogenous proteins. By contrast, when its effect is studied in an *in vitro* system (for example, when globin mRNA is injected into *Xenopus* oocytes), only the synthesis of globin is increased.

In *Nature New Biology* next Wednesday (November 28) Giglioni *et al.* describe some experiments designed to help elucidate the function of haemin in globin synthesis. Using the oocyte system they have found that in conditions of rabbit globin mRNA saturation there is about four times more β globin than α globin synthesised. By increasing the amount of haemin added to the system α globin synthesis is proportionally increased until a haemin concentration of 30 μ M when the ratio remains constant with α globin nearly 40% of the total globin synthesised in the system.

Endogenous protein synthesis is unaffected even at high haemin concentrations. At subsaturating levels of mRNA an α : β globin ratio of 1:1 can be achieved by injecting haemin into the oocytes, and if globin mRNA rich in α messenger is used more α than β is synthesised.

From these results alone, the possibility cannot be excluded that haemin affects the recovery of the globin chains, after their release from the ribosome, rather than their synthesis. The results of control experiments, however, make the first suggestion extremely unlikely. Control experiments also exclude the possibility that the low α to β ratio, in the absence of haemin, is due to a delay in the release of α chains relative to β chains.

It seems clear that in this system haemin controls the synthesis of α but not β mRNA. The authors suggest that the mRNAs for α and β globin compete for some component necessary for their translation (but not that of endogenous mRNAs), and that the effect of haemin is restricted as soon as mRNA concentration becomes saturating.

It is difficult to know how far these results can be extrapolated to explain the action of haemin in intact reticulocytes. If reticulocyte-rich blood is incubated in the presence of lead the synthesis of haemin is inhibited and this is followed by a 90% reduction in globin synthesis. The absence of haemin in the oocyte system does not have such a depressing effect. In haemin-free reticulocytes, however, the α globin synthesis is inhibited more than that of β globin so that in this important aspect the oocyte system and reticulocytes are the same.

obtained about the menstrual cycle, its pattern and time of the last menstruation before rape. Analysis of these conceptions showed that 33–46% of all conceptions took place during the safe period after menstruation, 10–30% during the safe period before menstruation and about 8% during menstruation itself. Thus fertility seemed to be elevated during most of the first half of the cycle and not only at about mid-cycle. (2) Conceptions resulting from limited exposure. An evaluation of 100 carefully selected cases showed that the risk of conception during the first and last four-day period of the menstrual cycle could be as high at 10% of the risk of conceiving during the mid-cycle period. In an investigation involving 241 British women who were using the basal body temperature method for birth regulation and who were studied throughout nearly 2,000 cycles, the conception risk was highest between days 10 and 12 of the cycle. The risk, however, was still very high at any time from day 5 to day 15 and, although markedly reduced during the luteal phase, the risk could still be up to 5%.

The value of this type of evidence depends on the surety that no other cohabitations took place during the period in question. Conceptions occurring in women with amenorrhoea have also been reported, although such evidence is difficult to evaluate in view of the possible spontaneous ovulation which occurs occasionally in these subjects.

Jöchle, after reviewing the evidence, concludes "the possibility of coitus-induced ovulation in humans should no longer be denied" and consequently it makes one sceptical whether the rhythm method of contraception can ever be completely successful. Most of the evidence quoted, however, is circumstantial; much less doubtful evidence is required before coitus-induced ovulation can be accepted as a reality.

PROTEIN SYNTHESIS

Ribosome Attachment

from a Correspondent

JOAN ARGETSINGER STEITZ has continued her studies on the control of the initiation of protein synthesis in the small RNA bacteriophage called R17. She had previously determined the nucleotide sequence of the three initiator fragments of the RNA, each about thirty residues long, which are responsible for the attachment of the RNA to the ribosome of the infected cell. These three fragments correspond to the three proteins, the coat protein, the replicase protein and the A protein, synthesised by the RNA.

She has now studied the interaction of the short thirty-residue long initiator

fragments rather than the intact 3,300-residue long RNA molecule, with ribosomes (*Proc. natn. Acad. Sci. U.S.A.*, **70**, 2605; 1973.) Surprisingly, only the initiator fragment for the A protein has the ability to bind *in vitro* to either *Escherichia coli* or *Bacillus stearothermophilus* ribosomes. By contrast, the initiator fragments for the coat and replicase protein do not bind significantly. She concludes that the RNA ribosome binding site of the A protein seems intrinsically to be a good initiator, whereas efficient recognition of the short coat and replicase regions requires the participation of some portions of the remainder of the phage RNA molecule.

Steitz suggests in a discussion that the influence of these other parts of the RNA on the specific initiator regions is probably exerted by a control of the exact three-dimensional structure of the binding sites. The inability of the coat protein site to bind, however, was surprising as it is known to form a stable hairpin-looped secondary structure with an A-U-G codon (specifying the first amino acid, formyl methionine, of the coat protein) exposed in the loop. Presumably therefore this loop formation cannot be sufficient for recognition by ribosomes. In fact, as such a stable hairpin-looped structure is unlikely to be present for the A protein site in either the fragment or the intact molecule, Steitz suggests that the function of

the remainder of the R17 RNA molecule may actually be to facilitate opening of looped structures during ribosome attachment.

INSECT PHYSIOLOGY

Juice Extractor

from our Insect Physiology Correspondent

SINCE Léon Dufour in 1833 published his observations on the anatomy of the gut in the Homoptera, it has been known that most members of this group of plant-sucking bugs have a more or less complicated association between the commencement of the midgut and its termination, in conjunction with the Malpighian tubules, in the ileum (the first segment of the hindgut). Dufour named this arrangement the 'filter chamber' in which, as he supposed, the copious watery contents of the plant juices were filtered off directly to the hindgut, while the nutrient material was carried on to the midgut. But there have been no experimental studies carried out to substantiate this idea.

A physiological study of the kind required has now been made by Cheung and Marshall (*J. Insect Physiol.*, **19**, 1801; 1973) on a variety of cicadas in Hong Kong and Australia. Cicadas feed on xylem fluid which is hypotonic to the haemolymph of the insect and contains high concentrations of potas-

Soft Gamma-ray Bursts from Compact Objects

THE energetic soft γ -ray bursts observed by the Vela satellites could result from fleeting episodes of accretion on to nearby compact objects—neutron stars or black holes. The sixteen or so bursts seen so far last typically for 1 to 10 s and show significant structure on time scales as short as 100 ms. The uniform distribution of possible source locations over the sky suggests that the sources are local.

Taking the typical distance as 100 pc, the luminosity during each burst is about 10^{37} erg s⁻¹, with the radiation spectrum peaking at around 100 to 400 keV. In *Nature Physical Science* next Monday (November 26) Lamb, Lamb and Pines emphasise that these time scales and luminosities are characteristic of the compact galactic X-ray sources, which are thought to be neutron stars or black holes continuously accreting matter from their close stellar companions.

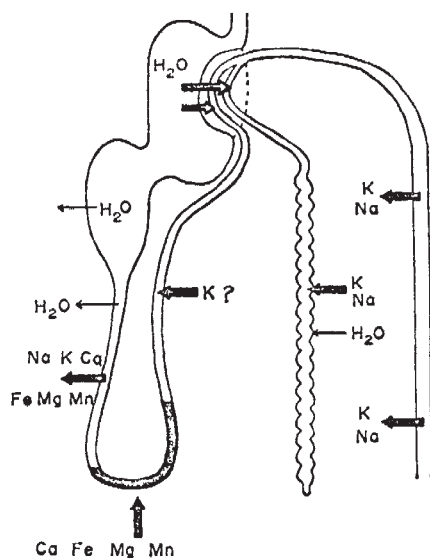
The space density of these X-ray sources is less than 10^{-8} pc⁻³. The authors, however, estimate the sources of the γ -ray bursts to have a space density of about 2.5×10^{-2} pc⁻³ and argue that the space density of binary systems containing a compact object could well be comparable.

The amount of matter that has to be accreted in order to liberate the required amount of energy per burst is about 10^{16} g. The largest solar flares, occurring every 5 to 20 yr, eject a mass of about 10^{16} g at a speed of about 1,500 km s⁻¹. Thus if the binary companion of the compact object undergoes similar flaring activity—perhaps on a slightly larger scale, but not necessarily as violently as flare stars—accretion of a part of this ejected material can neatly account for the observed properties of the soft γ -ray bursts. Since the ejection velocity is so supersonic, the accreted material need have little angular momentum with respect to the compact object, and so is able to fall straight on to the surface without having to go through the relatively slow process of forming an accretion disk.

In ordinary X-ray sources with temperatures corresponding to about 10 keV, the energy liberated by the continuously infalling material is more or less thermalised on the surface. It seems plausible that the energy liberated by a single blob of matter falling on to the surface will be less completely thermalised and will, therefore, be radiated at the higher temperature corresponding to soft γ rays.

sium, sodium, calcium, magnesium, chloride and phosphate ions. The urine contains the same ions in slightly lower concentrations. Amino acids and sucrose are present, and traces of amino acids persist in the urine. If xylem fluid is injected into the oesophagus there is an immediate ten-fold increase in the flow of liquid in the ileum. Meanwhile the osmotic pressure in the xylem fluid within the filter chamber rises, while the osmotic pressure in the anterior part of the ileum rapidly falls.

As the residual fluid passes on down the midgut, water, nutrients and ions are absorbed into the haemolymph and divalent ions are stored in granular form in the walls of the mid-midgut. Ions may be transferred from the haemolymph into the posterior tubular midgut, where the osmotic pressure of the contents is high in the post-feeding stage. Certainly the Malpighian tubules secrete a fluid which is rich in potassium (42 mM/l) and sodium (15 mM/l) and is hypertonic to the blood. Thus when the contents of the terminal midgut and of the Malpighian tubules reach the filter chamber and become intimately associated with its walls, they have an osmotic pressure considerably higher than that of the xylem fluid as it enters the filter chamber proper. Passive osmosis will therefore occur and water will thus be carried across the walls into the commencement of the ileum. Potassium and to a lesser extent sodium, as in other insects, are actively reabsorbed in the lower segments of the ileum and thus provide the recircling ions needed to keep the machine going.



Suggested ion and water movements in the cicada gut.

These results strongly suggest that Dufour was right and the chamber really is a 'filter chamber', and that the ionic concentrations needed to sustain its operation are the result of secretory activity elsewhere in the Malpighian tubules and the regions of the gut wall.

SILICA

Light Thrown on Charge Transport

from our Solid State Physics Correspondent

THE observation of currents in insulators has always been a difficult task and thus it is only recently that it has been confidently asserted that electrons travelling in solids with wide band gaps do so according to roughly the same laws as those in semiconductors, and that, given the necessary boost, electrons in solid dielectrics can be raised from the valence states to a conduction band and, in the right material, can then move easily and without undue scattering or trapping over large distances. Such evidence can only be gained by the use of high energy sources of light or particles and, preferably, very short pulses. Spear (see, for example, *Phys. Rev. Lett.*, **25**, 509; 1970) pioneered this work, deducing drift mobilities for electrons in such materials as Pyrex glass. From his technique, however, it was not easy to deduce basic quantities such as carrier lifetime and trapping frequency. Recently, Hughes (*Phys. Rev. Lett.*, **30**, 1333; 1973, and *Proc. Twenty-seventh A. Symp. Frequency Control*, Cherry Hill, New Jersey, June 1973) has greatly reduced the time scale by using very sharp X-ray pulses lasting only a few nanoseconds together with equally fast signal-recording techniques. So, for the first time, a carrier lifetime for silica has been obtained and an interesting array of effects has been revealed.

Application

These experiments are illuminating and important because silica is a particularly useful material both in the research and technological sense. The structure of silica, in crystalline and amorphous forms, has been intensively examined by diffraction techniques and the Si-O bond as a chemical entity is also much studied by organosilicon chemists. Silica is of great importance in technology—its uses range from rugged, expansion-free optics to crystal oscillators; further, silica has recently found new and important uses as a key element in metal-oxide-silicon devices, surface acoustic wave devices, optical waveguides and pressure gauges. Also, being a refractory, insulating material, silica may play a significant part in the building of a nuclear fusion reactor and indeed already provides the most long lived thermal protection for space vehicles exposed to intense radiation in space. The combination of strong piezoelectric response, optical transmission and controlled transport properties may also give silica an important place in optical integrated circuits. Thus, it is important to learn as much as possible about how charges and ions move in this material.

The band gap of amorphous silicon

dioxide in thin-film form has been determined to be about 9 eV. It is known that intrinsic d.c. photoconductivity can be induced in the material and that the mobility of electrons is high, by contrast with that of holes which is much lower. The electron mobility in thin-film silicon dioxide is of the order $30 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ (Williams, *Phys. Rev.*, **140**, A569; 1965). This is a very high value for an amorphous material since Mott (*Adv. Phys.*, **16**, 49; 1957) estimates that a typical electron mobility for amorphous materials is about $1 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$. Thus, there is the extra interest of a new measurement of charge transport in a bulk solid that it may at least confirm or contradict this surprising measurement and, furthermore, allow the measurement to be done on both crystalline and amorphous forms, a comparison not possible with thin-film silica.

A very high peak dose rate of X rays must be used, since, even with, say, $10^{10} \text{ rad s}^{-1}$ of 600 keV photons, the transient currents generated are small (of the order of a few nanoamps) and flow for a very short time (of the order of 10 nanoseconds). These measurements are, however, well within the bounds of the capabilities of Sandia Laboratories. Sandia is, in fact, interested in the possibly catastrophic effect of electric fields that are high enough to produce breakdown in quartz crystal oscillators or pressure gauges. Hughes has been able to distinguish between two forms of decaying current after the X-ray pulse and to distinguish cases in which the drift mobility is field dependent and others in which it is not. This is vital information, since the former condition indicates that many carriers are managing to transit the sample without being trapped, whereas the latter case indicates trap modulation in some samples, from the characteristics of which a carrier lifetime can be deduced. There is also a long lived component of the photocurrent which could represent an important check on a recent theory of radiation-induced ion mobilisation (McCaughan and Murphy, *IEEE Trans. Nucl. Sci.*, **NS19**, 249; 1972). The most satisfying result is for very pure amorphous fused silica. As with the thin-film samples already mentioned, Hughes finds the carrier mobility in a bulk fused silica slab to be about $20 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ at room temperature, increasing at lower temperatures to a saturation level of about 40. Not only does this fit well with the thin-film data but also with a theoretical prediction of Lynch (*J. appl. Phys.*, **43**, 3274; 1972) in which the temperature dependence is determined by longitudinal optical (LO) phonon scattering alone and predicts $32 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ at room temperature. Lynch's theory

also correctly predicts the breakdown strength of silicon dioxide films—another indication that these measurements should rapidly find practical application.

Mobility and Lifetime

Surprisingly, mobility and lifetime are lower in crystalline silica and, although it is difficult to control the incorporation of impurities during the growth of quartz crystals, a correlation of carrier lifetime and mobility with degree of impurity of crystal seems to exist. For example, Hughes finds that lithium-doped synthetic quartz has a higher mobility-lifetime product than the non-doped variety, whereas the synthetic fused silica samples, always much more pure than the flux-grown crystals, typically have twice the carrier lifetime of the crystals and well over twenty times the mobility value. Although the reduced mobility might suggest trapping phenomena as the cause, the mobility exhibits little temperature dependence. Thus, the more likely explanation is some form of impurity scattering, as confirmed in semiconductors. The field dependence of the radiation-induced conductivity again suggests LO phonon interaction as the limiting effect, since the drift velocity saturates at about the levels predicted by Thornber and Feynman (*Phys. Rev.*, **B1**, 4099; 1970), around 10^7 cm s⁻¹.

The question, then, is why an amorphous solid should possess such high mobility—indicating a mean free path of about 40 Å—when, according to most theories of the amorphous state, the mean free path should be of atomic dimensions, on account of the presence of localised states induced by the presence of disorder (see, for example, the studies on amorphous silicon by Spear and Le Comber, *J. Non-cryst. Solids*, **8-10**, 727; 1972). This would seem to confirm the X-ray evidence (Konnert, Karle and Ferguson, *Science*, *N.Y.*, **179**, 177; 1973) that the short-range order in fused silica is very good, the only deviation from order being some variation in Si-O-Si bond angles. This probably means that there is not a large amount of bond strain in the atomic network, therefore the same wide distribution in binding energies found in many amorphous solids does not exist. This could well lead to a major reduction of the 'tail' of localised states normally required to explain the transport and optical properties of compounds like the chalcogenide glasses.

Certainly, the reflectance spectra of fused silica and quartz look astonishingly alike (Phillipp, *J. Phys. Chem. Solids*, **32**, 1935; 1971) and some might say that the high mobility suggests that silica borders on the microcrystalline. But just as melting produces no strong discontinuity in the conductivity of good

conductors (see, for example, Adler, *Crit. Rev. solid state Sci.*, **2**, 317; 1971), it may be that electron transport continues to be efficient whenever short range order persists and thus so far the picture of fused silica as an amorphous solid remains. It should also be said that Hughes finds that holes seem to be very firmly lattice trapped and do not contribute at all to the photoconduction. This confirms most previous findings in thin-film silica and lends support to the current theories of space-charge build-up in these materials (see, for example, Zaininger and Holmes-Siedle, *RCA Rev.*, **28** (2), 208; 1967).

Implications

One general conclusion is that it may take as much (or more) trouble and time to obtain insulator crystals free of troublesome impurities as it did for semiconductors especially since, at the moment, there is not as strong a technological motivation for producing them. For those concerned with controlling radiation-induced conductivity (reactor designers and so on) manipulation of impurity scattering may, however, provide a useful tool for reducing unwanted conductivity. Second, one can echo a conclusion of Revesz (*J. Non-cryst. Solids*, **7**, 435; 1972) that the amorphous oxides, nitrides and related glasses might provide a good medium for the basic

study of the amorphous state because they are disordered only in the mildest way possible. Third, low field conduction work has received encouragement from these findings, which have tied together and strengthened some previously intriguing but hardly demonstrable hypotheses on transport in insulators and, incidentally, have annihilated at least one earlier theory of field dependence of mobility in silica (Onnasch, *Phys. stat. sol.*, **38**, 579; 1970).

PALAEONTOLOGY

Fossil Diversity

from a Correspondent

It is widely acknowledged that plate tectonics has had a revitalising effect on many fields of earth science, and nowhere is this more true than in palaeobiogeography, which is the name given to the study of fossil distributions in time and space. Abundant evidence of the burgeoning interest in this subject is provided by the numerous papers recently published in the *Atlas of Palaeobiogeography* (edit. by A. Hallam, Elsevier, 1973), and in two conference symposia, *Organisms and Continents Through Time* (edit. by N. F. Hughes, *Paleont. Ass. Spec. Paper* 12, 1973) and *Implications of Continental Drift to the Earth Sciences*, vol. 1 (edit. by D. H.

Rock of Grenville Age found on Rockall Bank

GEOPHYSICAL evidence suggests that the Rockall Plateau (and thus the Rockall Bank which forms part of it) may be a microcontinent isolated during one of the phases of spreading in the North Atlantic region. Until recently, however, geological evidence for a continental basement structure in the form of granitic or metamorphic rocks on the plateau was not entirely convincing, because, although several dredge hauls had been carried out in the vicinity of the plateau, most of the recovered samples could not be interpreted unambiguously. Moreover, further ambiguity was introduced by the presence of iceberg plough marks around the Rockall bank and evidence of ice-rafted deposition.

This equivocal situation was resolved earlier this year when Roberts *et al.* (*Nature phys. Sci.*, **244**, 21; 1973) reported the results of drilling two outcrops about 100 km apart in the southern section of the Rockall Bank. Granulite facies metamorphic rocks were found at both sites. In one case the hornblende in the drill core (acid granulite) was dated at 1566 ± 33 million years (Loxfordian) and the whole rock at 1670 ± 24 m.y. Thus the presence of continental rocks underlying the Rockall Bank was confirmed, suggesting, by ex-

tension, that the whole Rockall Plateau may indeed be a microcontinent.

But Roberts and his colleagues also proposed that rocks of Grenville age may occur on the southern section of the Rockall Bank—a prediction arrived at by considering the pre-drift reconstruction of the North Atlantic Ocean in the light of the new Loxfordian age. This prediction has now been confirmed by Miller, Roberts and Matthews who report their discovery in *Nature Physical Science* next Monday (November 26). The rock concerned, an andesine-orthopyroxene-biotite-quartz granulite, is that obtained previously by Roberts and his colleagues at the southernmost of their two sites on the southern section of the Rockall Bank.

This age obtained (987 ± 5 m.y.) is the first Grenville age found within the British Isles or west of the Caledonian Front in Europe and suggests that the Grenville Front crosses the southern section of the Rockall Bank, although confirmatory results from other rock samples will be required before certainty can be claimed. In the meantime, however, Miller and his colleagues make a further prediction—that rocks of Grenville age may also underlie parts of the Porcupine Bank or the continental shelf off Northern Ireland.

Tarling and S. K. Runcorn, Academic, 1973). Most of these articles are concerned with patterns of organic provinciality or cosmopolitanism in relation to migrating continents. Another fruitful line of approach, however, has been to consider how fossil diversity, or taxonomic variety, might have been affected by plate movements in the past 600 million years.

Pioneer work in analysing diversity changes through Phanerozoic time in fossil marine invertebrates has been undertaken by the American palaeontologist J. W. Valentine. In a series of stimulating papers during the past few years, he has put forward interpretative models which attempt to relate the diversity patterns recognised to changing configurations of continent and ocean, and changing climate. A particularly commendable feature of his work has been the successful application of modern ecological concepts such as environmental stability to the fossil record.

Valentine recognises a rapid rise in the number of families and genera in the Cambrian and early Ordovician, reaching a maximum in the Devonian, followed by a progressive decline to a minimum in the late Permian and early Triassic. Subsequently diversity

seems to have increased at a high rate through the remainder of the Mesozoic and Cainozoic. The Palaeozoic and Cainozoic provinciality patterns are held to be quite different. During the Palaeozoic the existence of a huge supercontinent, and hence low environmental stability, centred around the South Pole favoured high climatic continentality and a mild thermal pattern of relatively low provinciality, also helping to limit diversity. In the Cainozoic high provinciality (and hence diversity) developed as a consequence both of dispersion of continental masses and stronger latitudinal differentiation of climate. The sharp drop in diversity at the end of the Palaeozoic is attributed to widespread extinction resulting from the creation of the supercontinent of Pangaea, by the suturing of several smaller continents, which led to increased interfaunal competition and to increased seasonal contrasts in climate.

Diversity changes through time can be considered in terms of secular trends and shorter-term oscillations. With regard to the former, Raup (*Science*, N.Y., **177**, 1065; 1972) has questioned the pattern of changes outlined by Valentine by drawing attention to several possible time-dependent biases in the data.

To take one example, the chances of given fossil taxa being preserved will depend to a large extent on the chances of their containing sediment not being subject to erosion or metamorphism. Quite simply, these chances increase with decreasing age, hence the sharp and progressive diversity increase in the Mesozoic and Cainozoic could be an artefact, as could the late Palaeozoic diversity reduction, which seems to correlate well with a reduction of volume of marine sediment deposited at that time. Raup proposes an alternative model in which a mid-Palaeozoic diversity maximum is assumed, followed by reduction to an equilibrium level. He has generated a computer model on this basis, with the hypothetical diversity being modified by selective fossil destruction, the probability of which has been calculated to decrease through the course of time.

Raup is probably correct in claiming that Palaeozoic diversities were relatively higher than appear from Valentine's data, and that the strong post-Triassic increase may to some extent be an artefact. Since, by general consent, the end of the Palaeozoic marked a time of mass extinction with its obvious concomitant of reduced diversity, one must react more sceptically to Raup's postulated correlation with reduced marine sediment volume, which may be controlled by the same fundamental cause or be merely coincidental. His criticisms have less bearing, moreover, on the interesting and comprehensive work of Flessa and Imbrie (in the Tarling and Runcorn volume), which is concerned not with secular trends but with oscillations in diversity at intervals of 10 million years.

Flessa and Imbrie apply Q-mode factor analysis to rates of increase and decrease of many fossil invertebrate and vertebrate families, the fluctuations in numbers being treated as a function of rates of origination and extinction. Their analysis confirms earlier, less quantitative notions that the fluctuations of different groups are not random but tend to coincide in time. The conclusion is drawn that correlation with events associated with lithospheric plate movements is sufficiently good to suggest a significant relationship. Flessa and Imbrie go on to develop a predictive model for changing continent-ocean relationships based on the ecologists' well-known species-area equation. Graphs are produced showing the changes in diversity to be expected for a given change of continental area and differing degrees of cosmopolitanism and geographic isolation. In spite of the speculative nature of the exercise and the simplifying assumptions made, their analysis is very enlightening and suggests a promising line of investigation for the future.

SELENOLOGY

Near-surface Model

from our Geomagnetism Correspondent

ESTIMATES of the physical properties of the near-surface material of the Moon were made even in the days when the only data available were measurements of the brightness temperature of the lunar surface. Thus, for example, Piddington and Minnett (*Aust. J. scient. Res.*, **2A**, 643; 1949) proposed that the lunar surface comprises a thin (about 1 mm) layer of fine powder covering a more solid base. Jaeger (*Aust. J. Phys.*, **6**, 10; 1953) also concluded that the lunar surface is a fine evacuated powder, or at least acts like one thermally, to which Muncey (*Aust. J. Phys.*, **16**, 24; 1962) added a high conductivity substrate. A few years later, Linsky (*Icarus*, **5**, 606; 1966) suggested that the thermal conductivity in the upper few centimetres may be significantly temperature dependent.

So how do these older, pre-Apollo conclusions compare with those based on newer, more comprehensive measurements *in situ*? Keihm *et al.* (*Earth planet. Sci. Lett.*, **19**, 337; 1973) have now combined *in situ* measurements of lunar surface brightness temperatures at the Apollo 15 Hadley Rille landing site, data from five thermocouples lying on or just above the surface at the same site, and a density profile and a heat capacity function derived from other

Apollo data, to produce a model of the upper few tens of centimetres of the lunar regolith having the following characteristics.

The upper layer of the surface is about 2 cm thick and is strongly insulating, having a mean thermal conductivity in the range $0.9\text{--}1.6 \times 10^{-5} \text{ W cm}^{-1} \text{ K}^{-1}$ (*sic*). Below this surface layer there is a large conductivity gradient, resulting in a mean conductivity of $5.5 \times 10^{-5} \text{ W cm}^{-1} \text{ K}^{-1}$ at 5 cm depth; but at greater depths the conductivity increases more gradually to $1.4 \times 10^{-4} \text{ W cm}^{-1} \text{ K}^{-1}$ at 49 cm. In the upper few centimetres the conductivity is also strongly temperature dependent, and about 70% of the heat transfer at the highest temperatures is by radiation between particles.

The temperature dependent conductivity close to the surface is required to explain an observed high temperature gradient (an increase of 47 K in the upper 83 cm) and indicates the presence of very loosely packed material in the upper few centimetres. Since the particle configuration and degree of compaction in such material will be difficult to maintain once the material is moved, Keihm and his colleagues conclude that measurements made on returned lunar samples may indicate properties significantly different from those of the undisturbed lunar surface. This may be why their ratio of radiative to conductive heat transfer (at 350 K), for example, is almost twice that measured for returned lunar fines.

Submillimetre Astronomy

M. SIMON

Department of Earth and Space Science, State University of New York at Stony Brook, Stony Brook, New York 11790

Although astronomy at submillimetre wavelengths is still in its infancy, work in two different areas—observations of HII regions and molecular clouds, and observations of the temperature minimum in the solar atmosphere—is particularly advanced.

NEARLY two decades of the electromagnetic spectrum from 20 μm to 1 mm have been virtually inaccessible to the astronomer because of severe absorption by the Earth's atmosphere. This spectral region is of great interest, however, from observations of the 3 K background radiation on the cosmological scale, to observations of star formation on the galactic scale, and the atmospheres of the Sun and planets locally. Recently, the submillimetre region has begun to be explored using balloons, rockets and aircraft as observing platforms, and from ground-based observatories through several atmospheric windows. Although these windows are poor compared to the optical and near infrared windows, they are usable at observatories where the atmosphere is particularly dry. This article is a discussion of the present status of submillimetre work but I shall not discuss observations of the 3 K background radiation or of the planets, as these have been reviewed recently^{1,2}.

Transmission of the Earth's Atmosphere

Figure 1 shows the transmission of the Earth's atmosphere in the infrared and submillimetre regions based on refs 3–5 and our own experience. The principal source of absorption in the far infrared is water vapour, and the figure is an approximate representation of the transmission under conditions of 1 mm of precipitable water vapour. It is clear that the atmosphere is opaque in the 100 μm region so that astronomical observations have to be carried out from aircraft flying at the top of the troposphere, or from balloons and rockets at yet higher altitudes. There are rather poor atmospheric windows in the 30 μm region, and again at 350 μm and longer wavelengths. These are usable for astronomical observations at sufficiently dry observatory sites. Several groups have begun to observe in these windows.

Under good conditions, the atmospheric transmission in the windows at 350 μm , 450 μm , and 650 μm is sufficiently stable to be represented by the exponential extinction law $\exp(-\alpha(\lambda) l \rho)$, where $\alpha(\lambda)$ is the intrinsic extinction coefficient, l the air mass in the line of sight, and ρ the precipitable water vapour. As it is notoriously difficult to estimate the atmospheric precipitable water vapour content, especially in night observations, I hesitate to quote absolute transmissions in these windows as a function of precipitable water vapour. The transmission at 350 μm is 30% for approximately 1 mm of precipitable water vapour in the line of sight (the uncertainty is in the calibration of the spectral hygrometer). Our measurements of the relative transmissions in these windows⁶ show that $\alpha(650 \mu\text{m}) = \alpha(450 \mu\text{m}) =$

$\alpha(350 \mu\text{m}) = (2.2 \pm 0.1)\alpha(1,000 \mu\text{m})$. From limited data from the few occasions when submillimetre observations, and 20 μm observations by the University of Hawaii group, were carried out simultaneously at Mauna Kea observatory, we estimate that $\alpha(350 \mu\text{m}) = (4 \pm 0.5)\alpha(20 \mu\text{m})$.

Galactic Sources

Direct observations of the emission of the coldest regions of our Galaxy must be made in the far infrared. Far infrared emission has been detected from HII regions and from regions of molecular emission at microwave frequencies. These observations are valuable for determining the total energy budget of these regions and the temperature and density of the interstellar dust in them. So far most observations have been in the 100 μm region from airborne platforms. Recently many of the same sources (as well as new sources) have also been observed at 350 μm and 1 mm. The telescope aperture in the ground-based observations is generally much larger than that available to the airborne work, so the observations at 350 μm and 1 mm have the advantage of much higher diffraction-limited spatial resolution. The sources are characterised by prodigious fluxes in the far infrared: for example, the 100 μm survey of 750 square degrees principally along the galactic plane carried out⁷ to a limiting sensitivity of $10^{-22} \text{ W m}^{-2} \text{ Hz}^{-1}$ yielded seventy-two sources. Of these, forty-six are clearly identified with HII regions (which in many cases contain radio molecular sources). Significantly, only one source discovered in the survey is possibly associated with a stellar object. Far infrared astronomy of galactic objects is thus distinctly the astronomy of extended objects. There is strong evidence that the emission of these objects is continuum emission since observations at 100 μm of a

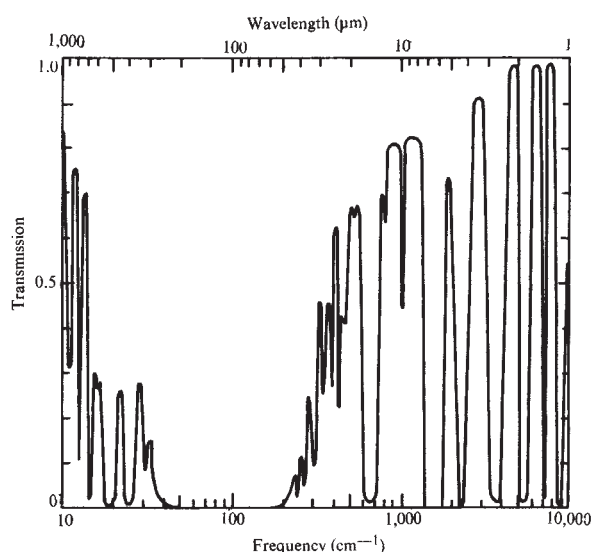


Fig. 1 Transmission of the Earth's atmosphere at infrared and submillimetre wavelengths. The transmission is intended to be roughly representative of conditions of 1 mm precipitable water vapour.

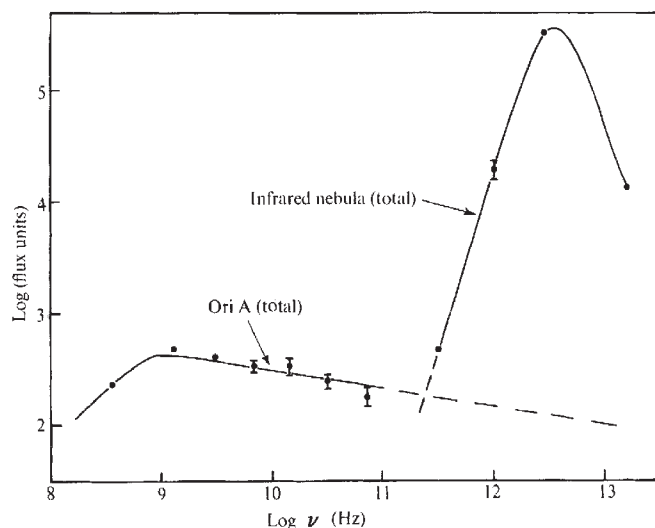


Fig. 2 The spectra of the total radio free-free continuum flux density of Ori A, and the total submillimetre flux density from the Kleinmann-Low infrared nebula. As discussed in the text, the positions of the strongest emission from Ori A and the infrared nebula are separated by about 1 arc min. The submillimetre data are discussed in the text, and the radio data are from refs 43 and 44.

given source (for example, the well studied sources in Orion and the galactic centre regions) by different observers with similar beamwidths but differing spectral bandpasses yield similar flux densities⁷⁻¹⁹. As dust is present in HII regions, and as many of the far infrared sources are also molecular sources (the dust is implicated as the catalytic agent in molecule formation), the most reasonable assumption is that the far infrared emission from these sources is the thermal emission of the dust grains. As I shall discuss later, the 20 μm , 100 μm , 350 μm and 1 mm data from the Orion far infrared source fit a thermal emission model quite well.

The mechanism of the heating of the dust is still poorly understood. The two possibilities considered involve very different assumptions about the nature of the far infrared sources. In the first, the emission is presumed to originate in a dusty Stromgren sphere^{8,11,13}, so that the HII region, as delineated by its Lyman continuum, and the far infrared source should be spatially coincident. In this model the heating of the grains is due to Lyman α radiation of the gas and direct radiation from the exciting stars. Supporting this view, Harper and Low⁸ in their original observations of HII regions in a 40 to 750 μm pass band found a rough proportionality between the observed far infrared flux and the free-free continuum flux density at 2 cm. Similar correlations have been found by the other groups^{11,14} observing HII regions at 100 μm . But all observers find that the Lyman α energy available (as estimated from the excitation of the HII region) is less than the energy required to account for the far infrared flux by about an order of magnitude. Johnson⁴⁵ has shown that the total stellar luminosity and the far infrared are about equal in a number of HII regions. In the HII region M42 (in Orion), however, the exciting stars are separated by at least 1 arc min from the far infrared source so that it is not clear that the far infrared luminosity can be attributed to the energy input of the observed stars.

The other point of view is that the far infrared emission is not from dust in the HII region itself, but rather from dust in the dense molecular clouds that are associated with it¹⁵ (a detailed model of the possible association of the molecular cloud in Orion with the rest of the HII region is given in ref. 46 by B. Zuckerman). In this view, the heating of the dust grains could be caused by stellar or proto-stellar objects embedded in the cloud¹⁶. Ground based observations have shown indeed that the 350 μm emission in Orion (ref. 17

and unpublished work of D. Y. Gezari, R. R. Joyce, G. Righini and M. Simon) and DR21 (Rieke *et al.*⁴⁷) peaks at the position of the strongest molecular spectral line emission rather than at the peak of the radio free-free continuum. In Orion this emission is at the position of the strong 20 μm extended source discovered by Kleinmann and Low¹⁸, and in DR21 at the position of the OH source. The 1 mm emission from these sources also peaks at the positions (ref. 48 and private communication from P. A. R. Ade and J. D. G. Rafter). Similarly, Emerson *et al.*¹³ found that in several instances the peak of 100 μm emission from HII regions is displaced from the radio continuum peak.

Further high resolution observations in the far infrared are required to find the relative importance of these two contributions to the far infrared emission of HII regions, and very likely both processes will turn out to be important. For example, in an HII region such as M17, which does not (as far as is known) contain a very dense molecular source, and in which the strong 10 μm emission is coincident with the strongest radio-free emission¹⁹, the far infrared emission may well arise entirely from dust grains heated by ultraviolet radiation. Orion appears to have both kinds of sources. The Ney-Allen source²⁰, which peaks in the near infrared (this source is approximately centred on the Trapezium stars which are believed to be the exciting stars for the M42 nebula), can be accounted for naturally by emission from ultraviolet-heated dust. The second type of source is the Kleinmann-Low/molecular source which, as we have seen, gives rise to the far infrared emission. Finally, there are far infrared sources associated with dark clouds⁷ from which no radio free-free emission is known.

The two far infrared sources studied in greatest detail are the Kleinmann-Low/molecular source in Orion, and the complex of sources near the galactic centre. Figure 2 shows the spectrum of the total flux density of the KL source; as the source is extended, the plotted points are those believed to include the bulk of the flux from the source. The 20 μm total flux density is from Low²¹, the 100 μm flux density is from Hoffmann, Frederick and Emery⁷ and was obtained with a beam of 6 arc min, the 350 μm spectral point was obtained by Gezari *et al.* (unpublished) with a beam of 3.5 arc min, and the 1 mm flux density is the total obtained by Ade and Rafter (private communication) by mapping over an area of 4 arc min diameter. The 100 μm , 350 μm , and 1 mm points, of course, include both contributions from the Ney-Allen source and from the free-free continuum radio source. The former is quite negligible relative to the KL source at submillimetre wavelengths. The free-free contribution is certainly negligible at 100 μm and 350 μm , but it makes a significant contribution at 1 mm as indicated by the extrapolation of the radio-free emission in Fig. 2. Kleinmann and Low found that the observed flux density and size at 22 μm could be fitted by an optically thick thermal distribution ~ 70 K (ref. 18). The spectrum in Fig. 3 supports this interpretation. As the observed flux density decrease at wavelengths longer than 100 μm is steeper than the ν^2 dependence given by the Rayleigh-Jeans Law, the source must be optically thin with a frequency-dependent optical depth at these wavelengths. It may be shown (ref. 15 and unpublished work of Gezari *et al.*) from general considerations based on the Kramers-Kronig dispersion law that $\tau(\nu) \propto \nu^2$ in the long wavelength limit. Calculations of the optical depth of silicates²², based on measurements of the optical constants of silicates in the lunar soil²³, fit this low frequency behaviour well. Thus, in the low frequency limit, the flux density from an optically thin isothermal dust cloud may be expected to have a ν^4 dependence. (A temperature distribution within the cloud could make the frequency dependence less steep.) The submillimetre data in Fig. 2 at wavelengths longer than 100 μm fit this model well (when correction for the free-free contribution to the 1 mm flux density is made). The frequency-dependent opacity, of course, complicates determination of

the temperature of the source. Detailed analysis of this data shows (unpublished work of Gezari *et al.*) that the temperature is probably from 60 to 74 K, in agreement with the results of Kleinmann and Low, that the source is becoming optically thin at $100\ \mu\text{m}$ and that $\tau(100\ \mu\text{m})$ must be between 0.2 and 5. As the observations from which these conclusions are drawn represent fluxes from the entire source, the values of the parameters quoted here must be regarded as averages over the source. There is no difficulty in accounting for the high optical depths at submillimetre wavelengths. The molecular radio observations show that the molecular hydrogen density might exceed $10^7\ \text{cm}^{-3}$ in the core of the molecular source²⁴. Using typical values for the grain absorption efficiency for silicates, a normal gas-to-dust ratio, and grain mass density of $1\ \text{g cm}^{-3}$, one then naturally obtains values of $\tau(100\ \mu\text{m})$ of order 1 through the molecular cloud. Integrating the submillimetre spectrum in Fig. 2 and taking 500 pc for the distance to the Orion nebula, the total luminosity of the KL nebula/molecular source is $4.8 \times 10^{38}\ \text{erg s}^{-1}$. As noted by Hartmann¹⁶, this luminosity is several orders of magnitude greater than could be reasonably accounted for by the gravitational collapse of the cloud, and the most probable source of heating the cloud is the radiation of one or several early type stars.

A tentative general conclusion from this analysis of the radiation from the KL nebula/molecular source is that molecular sources known to be very dense (that is, sources in which transitions of molecules requiring high molecular hydrogen densities for collisional excitation are observed) may be expected to have high enough optical depths at submillimetre wavelengths to be strong submillimetre sources. This is indeed the case in W49, W51, DR21(OH), and Sgr B2 which have been detected from $100\ \mu\text{m}$ to 1 mm (refs 7, 8 15 and 47, and private communications from Ade and Rather and from M. W. Werner and P. M. Harvey).

The strongest far infrared source known, after the Sun and the Moon, is the complex region of the galactic centre. Its spatial extent, as revealed by the airborne $100\ \mu\text{m}$ observations, is $1^\circ \times 2^\circ$. Hoffmann, Frederick, and Emery²⁵ mapped this remarkable region at $100\ \mu\text{m}$ (Fig. 3) and found excellent agreement between the regions of far infrared emission and 2 cm radio emission, which is again free-free emission, except for the nonthermal source Sgr A. The peaks in their map also coincide with the known molecular clouds in this region. One of these, Sgr B2, is the richest source of molecular emission known²⁶, and has also been studied at $350\ \mu\text{m}$ (refs 14, 47 and unpublished work of Gezari *et al.*). The molecular source is quite large and probably has a dense core. The core is apparently smaller than 5 arc min and is probably about 1 arc min in size^{27,28} (at the distance of Sgr B2 this corresponds to ~ 3 pc).

The great spatial extent of this source makes comparison of different flux measurements (even at the same wavelengths) difficult for two reasons. First, the observed flux clearly depends very strongly on the beamwidth so the beam pattern must be known accurately in order to deduce the source brightness. Second, all the observations use some type of sky chopping scheme where the source signal is differenced against a position on the sky some distance away (usually small for technical reasons). This observing technique measures the derivative of the source brightness distribution. Clearly, chopping arrangements with large beam spacing (or, ideally, an absolute temperature reference as used in the rocket infrared observations¹³) are to be preferred. The present $350\ \mu\text{m}$ observations illustrate the difficulties of comparison of observations with different instrumentation. Observations of Sgr B2 with a 1 arc min beam and beam spacing of 4 arc min show a source of half power width ~ 3 arc min (N-S) $\times \sim 2$ arc min (E-W) and a peak flux density of about 8,000 flux units (Rieke *et al.*⁴⁷). On the other hand, observations of the same area with a 3.5 arc min beam and 10 arc min beam spacing indicate a peak of flux of

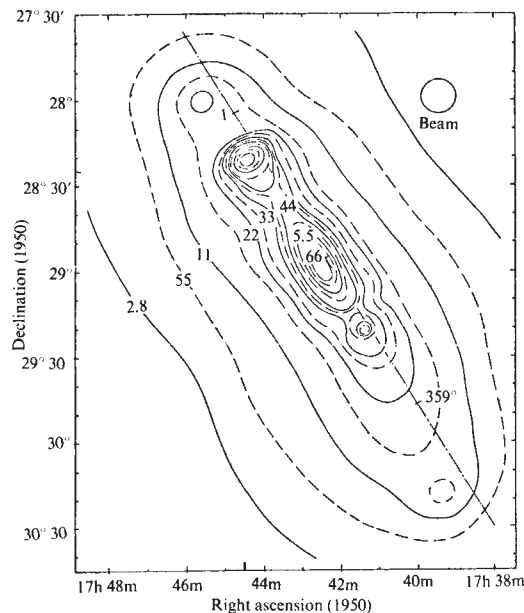


Fig. 3 Contour map of the galactic centre region at $100\ \mu\text{m}$ reproduced from ref. 25. The source Sgr B2 discussed in the text is within the northernmost of the three strong sources. (Reproduced with permission from *The Astrophysical Journal*, University of Chicago Press.)

$\sim 50,000$ f.u. and an extent 5 to 10 arc min E-W and about 10 arc min N-S (ref. 15 and unpublished work of Gezari *et al.*). These latter observations are in rough agreement with the structure in the $100\ \mu\text{m}$ map in Fig. 3. The two sets of $350\ \mu\text{m}$ observations are reconcilable and should be taken to be complementary. Thus the relatively small component is probably the dense core of the molecular source discussed already, and is seen superimposed on the more extended source.

Finally, it is interesting that the far infrared sources discussed so far have very little emission outside the $20\ \mu\text{m}$ to 1 mm band. At low frequencies, the approximately ν^4 flux density decrease makes detection difficult at radio wavelengths. For example, scaling the $350\ \mu\text{m}$ flux density of Orion to 3.5 mm suggests that the thermal emission from the dust in the molecular cloud should contribute only ~ 2 f.u. in a 3.5 arc min beam at 3.5 mm. Such a small contribution may be difficult to disentangle ambiguously from the very strong contribution due to the free-free emission. In a 3.5 mm survey of many far infrared sources, including Orion, Brown and Broderick²⁹ were unable to detect such an excess flux. It seems likely, however, that the upturn at 3.5 mm in the radio spectrum of the remarkable source Sgr B2 observed by Hobbs *et al.*³⁰ is from the tail of the far infrared emission. On the other hand, these sources are difficult to observe at wavelengths shorter than $20\ \mu\text{m}$ since their temperatures are so low. But submillimetre astronomy of galactic sources is still young, and the present results suggest that further observations will provide a valuable probe of the physical conditions in the cold components of the interstellar medium.

Solar Atmosphere

The radial temperature distribution of the solar atmosphere has a minimum between the photosphere and the corona in a region spanning nearly 500 km which is exceedingly difficult to study. Here I discuss the role of submillimetre observations in defining a model for the physical parameters in this region, their implications for the region's structure, and the potential contribution of these observations to the study of active regions.

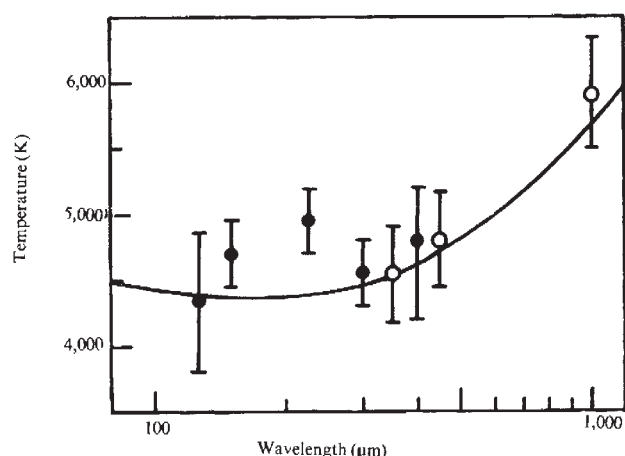


Fig. 4 The brightness temperature at the centre of the solar disk as a function of wavelength as given by the HSRA model³⁶. The data points are those published since the publication of the HSRA and are from ref. 6 (○) and ref. 37 (●).

The continuum radiation from the temperature minimum is assessable only in the rocket ultraviolet, or in the submillimetre region of the spectrum. The submillimetre continuum is perhaps more directly tractable since the source of opacity (free-free absorption due to the H^- ion) is well understood, and no strong emission features, unlike in the ultraviolet, are expected. Submillimetre observations of the solar brightness temperature as a function of wavelength at the centre of the disk may thus be inverted into the distribution of the temperature in the solar atmosphere as a function of optical depth. Submillimetre observations have already played an important role in this respect. Airborne observations in the 50 to 300 μm regions³¹⁻³³ and recent rocket observations³⁴ have indicated that the temperature minimum is 4,300 K rather than 4,600 K as had been previously inferred. This revision alleviates difficulties in understanding the 4,300 K temperature at the core of the Ca K line³⁵ and has been incorporated in the HSRA model of the atmosphere³⁶. Fig. 4 shows the temperature profile as a function of wavelength given by the HSRA model at submillimetre wavelengths. As the HSRA was adjusted to fit the best data available at the time, I show in Fig. 4 only measurements^{6,37} obtained subsequent to the publication of the HSRA. (Comparison of the HSRA with the data available at the time of its publication is in Fig. 2 of ref. 36.) The agreement of recent data with the HSRA is quite satisfactory. The strong upturn at $\lambda > 500 \mu\text{m}$ is dictated by the high brightness temperatures measured at 1 mm and longer wavelengths. There are no observations available of the brightness temperature between 500 μm and 1 mm, representing a factor of four in the optical depth, so data are needed to delineate the temperature distribution in this region.

Further information on the temperature distribution and structure of this region may be derived from the brightness temperature variation across the disk. For example, if the solar atmosphere is homogenous and spherically symmetric, the brightness temperature distribution should be entirely determined by the variation of central brightness temperature with wavelength, and the parameter $\lambda^2/\sqrt{(1-r^2)}$, where r is the fractional distance to the limb from the centre of the disk. In the HSRA model the temperature minimum occurs at about 200 μm . Limb darkening should be observed at longer wavelengths; the HSRA model predicts ~5% limb brightening at 350 μm at $r=0.8$. Our scanning observations at 350 μm appear to rule out this degree of limb brightening. Limb darkening at 1 mm has been reported^{38,39}, but recent observations at 1 mm, in which a detailed analysis of the beam pattern was made, seem to be consistent with no limb brightening at all (unpublished work of Ade, Rather and

P. E. Clegg). Departures from the limb brightening predicted by a homogenous model with the HSRA temperature profile may be interpreted in terms of either a revision of the temperature gradient in the HSRA, or a dropping of the homogeneity assumption. In view of the good agreement of the model with the brightness temperature measurements at the centre of the disk, and the well-known inhomogeneity of the solar atmosphere both above and below the region of the minimum, it is likely that here too the homogeneity assumption will have to be relaxed.

High resolution mapping observations at these wavelengths may also be expected to improve understanding of the electron density and temperature of active regions. Ade *et al.*⁴⁰ have mapped one active region at effective wavelengths 400 μm , 800 μm , and 1,200 μm , and found that the brightness temperature increased from 200 K at 400 μm to 350 K at 1,200 μm . These submillimetre observations may indicate the existence of a dense core of the active region that is nearly optically thick at these wavelengths. Further observations of active regions, and detailed comparison with radio observations, are clearly required.

Future Prospects

Submillimetre observations of extragalactic objects are still sparse, although the observations so far show it to be an area of great promise. NGC1275, M82 and 3C273 have been detected at 1 mm (unpublished work of Ade and Rather), NGC253 (Rieke *et al.*⁴¹) and possibly M82 (ref. 41) at 350 μm (although the flux calibration for M82 is almost certainly in error), and M82 and NGC253 at 100 μm (ref. 42). The millimetre wavelength radiation of sources such as 3C273 and NGC1275 is known to be non-thermal, and at least part of the flux is time-varying and believed to originate in rapidly-evolving small components. Observations of variability at submillimetre wavelengths would place severe restrictions on the models of these components. It is premature to speculate on the nature of the submillimetre radiation of objects such as NGC253 (which is the strongest extragalactic source at 10 μm) and M82, but the radiation may well be thermal.

Technically there are several promising areas. Fainter objects will become observable through the use of larger apertures and stabilised observing platforms in the airborne work, and the development of more sensitive detectors for both the ground-based work and airborne work (because in both the limiting noise at present is detector noise). This discussion of submillimetre astronomy is based on data obtained by broad-band photometry or very coarse resolution Michelson interferometry. There is a great incentive to develop submillimetre spectral line systems to observe fine structure lines, recombination lines, and molecular lines that are accessible in this region of the spectrum and to use them as astrophysical probes. Several active developmental programmes are under way, and it is probably not too optimistic to believe that in a few years the time will be right for a similar preliminary review of submillimetre line astronomy.

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Conditions Limiting Multiplication of Fibroblastic and Epithelial Cells in Dense Cultures

R. DULBECCO* & J. ELKINGTON

Imperial Cancer Research Fund, Lincoln's Inn Fields, London WC2

The multiplication of epithelial cells in plastic dishes is limited by the amount of plastic surface available per cell, that of fibroblastic cells by the availability of medium factors. Contacts between cells do not appear to limit the multiplication of either cell type. The multiplication of fibroblastic cells is even favoured by shorter intercellular distances, suggesting a distance-dependent helper effect between cells.

CULTURES of untransformed cells growing on a glass or plastic surface display the phenomenon of "density-dependent growth inhibition"¹: under standard conditions of

cultivation cell multiplication stops when a certain cell density, characteristic for each cell type, is reached. If a strip of cells is removed from a stationary culture, cells migrating from the borders into the denuded area (the wound) are activated to multiply, although the medium remains unchanged². It has been shown that the activation occurs when the cells leave the dense layer³. The differential ability of the cells in the wound to initiate DNA synthesis in comparison to those in the layer has been defined as topoinhibition⁴. Although topoinhibition is a useful parameter for characterising cell lines, especially in relation to transformation, its mechanism is undefined. The basic dilemma is whether the multiplication of cells in the layer is inhibited by the intimate contacts between cells ("contact inhibition of growth") or by a lower ability to utilise components of the medium, especially serum⁵. The reason for the uncertainty is that most experimental procedures affect many variables at once.

* R. Dulbecco is also a fellow of The Salk Institute, La Jolla, California.

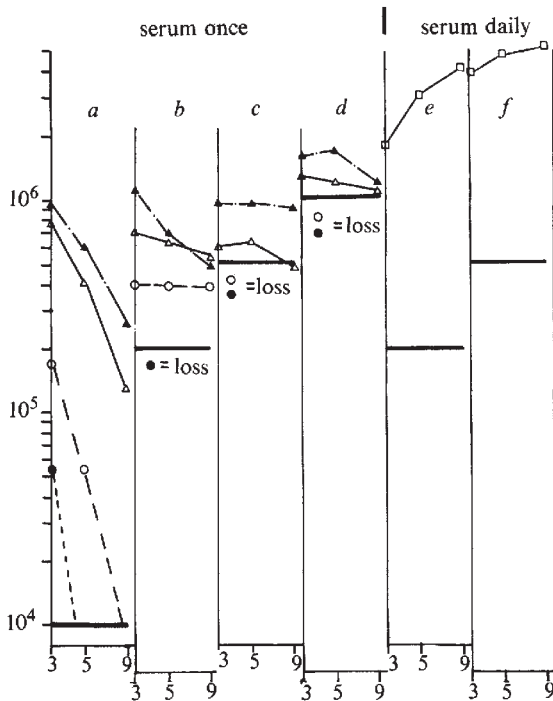


Fig. 1 Final number of Balb/c 3T3 cells in cultures of different size. Approximate dish diameters in centimetres are shown on the abscissa. *a* to *d*: Single supply of medium with the following concentration of calf serum: $\blacktriangle$, 20%; $\triangle$, 10%; $\circ$, 5%; $\bullet$, 2%. *e*, *f*: Daily change of medium with 10% serum. The number of cells in the inoculum of each set is indicated by the heavy horizontal line. The lines connecting cell numbers for different size dishes and the same concentration of serum terminate at the inoculum level when the next point is below that level, that is, there was loss of cells. Loss of cells at all three dish sizes for a certain concentration of serum is indicated by placing the symbol for that serum concentration below the inoculum line.

Varying Dish Size

The experiments we are now reporting are aimed at clarifying the role of cell-to-cell contacts under conditions in which the availability of medium is constant. To this end we have studied the effect of a single variable, the amount of dish surface available to each cell, on the number of cells present per dish at saturation, using the following scheme. Parallel cultures were prepared, each with the same number of identical trypsinised cells and in the same volume (6 ml) of medium (reinforced Eagle's containing calf serum at the indicated proportions), but in dishes (plastic, Nunc) of different sizes: 30, 50 and 90 mm in diameter. Hence the dish size was the principal variable. In the 30 mm dishes the depth of medium was about 7 mm, about 1 mm in the 90 mm dishes. The plastic area available to each cell in the 30 mm dishes was, on the average, about one-eighth that in the 90 mm dishes. The cultures were maintained in a CO_2 -flushed, high humidity incubator and were allowed to grow without medium changes until growth stopped, as shown by the absence of mitoses. The validity of this criterion was confirmed in some cases by growth curves. Usually, growth stopped somewhat sooner in the 30 mm dishes: 4 to 7 d, depending on initial cell density, compared with 5 to 10 d in the 90 mm dishes. After growth stopped, the cells were detached with trypsin and counted in a Coulter counter. Several cell lines were used: Balb/c 3T3 (ref. 6) and BHK 21 (Cl 13) (ref. 7), fibroblastic; CV-1 (ref. 8), and BSC-1 (ref. 9), epithelial; and SV3T3 (ref. 10) and Py BHK (produced in this laboratory), transformed. In different experiments the inoculum varied between 10^4 and 10^6 cells per dish, and the serum concentration in the medium between 2% and 20%.

In this protocol the main variable is the distance between cells, which in turn affects the extent of contact between them, their ability to move and to stretch. Two other variables, the depth of medium and possibly the nature of the plastic employed in the manufacture of dishes of different sizes, seem to be of little importance on the basis of internal controls, as indicated below.

The experiment has three possible outcomes. If the area of the plastic surface available to a cell limits cell multiplication, the final number of cells in a dish should be proportional to the surface of the dish. If, on the other hand, growth is limited by medium components, the final cell density should be equal on all size dishes. Finally, if there is a distance-dependent helper effect between cells (for instance, if growth is helped by cell-to-cell contacts or by labile substances produced by the cells), the number of cells should be inversely related to the dish surface.

The results with Balb/c 3T3 cells, which are characterised by a high topoinhibition and high serum requirement⁴, are given in Fig. 1*a* to *d*. When the cell inoculum and the serum concentration were high, the dependence of final cell number on dish size was that expected from limitation by medium. When the cell inoculum and the serum concentration were small, the relation conformed to that expected from a distance-dependent helper effect.

The latter result might also have been produced by loss of medium components to the walls of the dish, which would be more pronounced in the larger dishes. This possibility was tested by incubating the medium in the dishes for 3 d and then adding cells to it (5×10^5 per dish). The final number of cells per dish was about half that of similar cultures whose medium had not been preincubated, irrespective of dish size. Thus there is no evidence for loss of medium to the plastic, but only for partial inactivation. Conceivably, the effect may be due to loss to the walls of some growth factor present in the cell inoculum; but this possibility was not tested. Under no circumstance was there evidence that the available dish surface was limiting the growth of these cells.

The distance-dependent helper effect affects the growth rate of the cells, which is slower in the larger dishes (since they produce fewer cells in a longer time). The lower final cell number on the larger dishes may be due to greater inactivation of medium components, since a longer time is required to reach saturation.

We tested whether a dish surface requirement for Balb/c 3T3 cells became demonstrable when the availability of medium was increased by growing cultures with daily changes of 10% serum medium. As shown in Fig. 1*e* and *f*, these cells reached a resting stage with a larger number of cells per culture; but although the relation of final cell number to dish size showed some dependence on available surface, limitation of medium was still the most important factor stopping growth.

These experiments were repeated several times with similar results: similar results were also obtained with BHK cells.

Some other results of these experiments should be noted. In the first place, cultures with the same serum concentration and similar initial density of inoculum cells (and therefore similar helper effect) tended to yield similar (within a factor of two) final cell numbers irrespective of dish size (compare for instance points *d9* with *b3* and *b9* with *a3* in Fig. 1). This shows that the depth of the medium and the nature of the plastic have a minor importance for the final number of the cells. In the second place, when the ratio of cells to serum in the inoculum was small the final cell number was lower than the inoculum, indicating loss of cells. This result suggests that cell survival depends on a stoichiometric relationship between serum and cells. A stoichiometric relationship also holds between amount of serum and number of new cells produced, 0.06 ml serum corresponding to about 5×10^4 Balb/c 3T3 cells. This relationship

shows that the access of medium components to the cells is not affected by the degree of cell overlaps.

The epithelial cells of the BSC-1 and CV-1 lines, which have a high topoinhibition but a low serum requirement⁴, gave different results (Fig. 2). In all cases growth was limited primarily by the restriction of dish surface, especially when 10% serum was used. There was also, however, some medium limitation or helper effect because the cell numbers on 90 mm dishes were at most five times those on 30 mm dishes, although the dish surfaces differed by a factor of eight.

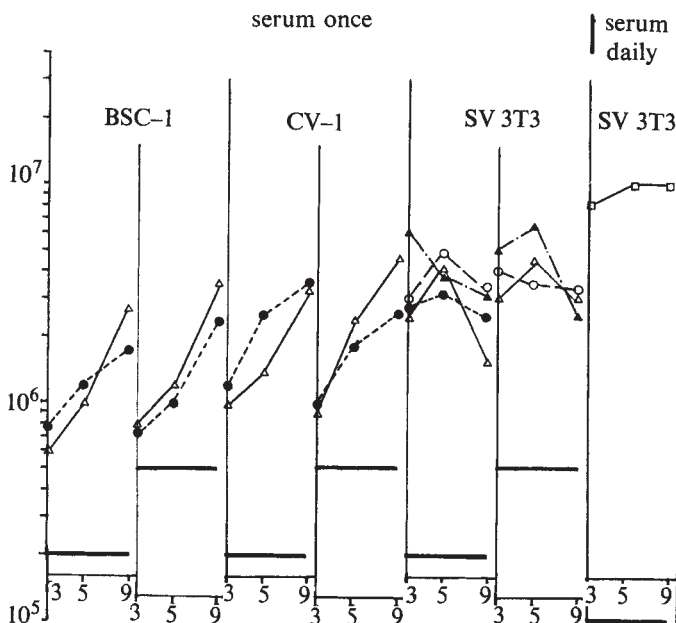


Fig. 2 Same as for Fig. 1, except for the last set, which had daily change of medium with 10% calf serum, there was a single supply of medium in all cases. For symbols referring to serum concentration see Fig. 1.

For transformed SV3T3 cells which have very low topoinhibition and serum requirements⁴ (Fig. 2) there was little effect of either the amount of serum or dish size in the range used. A similar result was obtained with Py BHK cells. With SV3T3 cells, changing the medium daily increased the final cell number to a constant value irrespective of dish size. Hence there is no evidence that these cells have a dish surface requirement even when medium is plentiful. It should be noted, however, that transformed cells did not attain a stationary stage: growth was stopped by the spontaneous detachment of the cells from the plastic.

Growing and Stationary Cultures

The result that under standard culture conditions multiplication of Balb/c 3T3 or BHK cells is not stopped by restriction of available dish surface shows that their growth is not limited by contacts between cells or by their inability to move or to stretch. Before this conclusion was used to explain the results of wound experiments, we examined the possible role of a difference in the two experiments. The present experiments study the effects of cell crowding on growing cultures, whereas the wound experiments employ already crowded and stationary cultures. The role of this difference was tested by varying the experimental procedure: Balb/c 3T3 cells were seeded in exhausted medium (originally containing 10% calf serum) obtained from confluent

resting cultures of the same cell type and diluted with the addition of fresh medium without serum (half the volume). The cells did not grow but formed stationary cultures. Then serum was added to a concentration of 10% to start growth. The results obtained were similar to those obtained by the standard procedure.

Fibroblastic and Epithelial Cells

These experiments suggest that cell multiplication is limited by different mechanisms in fibroblastic and epithelial cell cultures and, accordingly, that the significance of the wound experiment and of topoinhibition are also different.

With fibroblastic cells, a restriction of the available surface to which they adhere only begins to limit growth at extraordinarily high cell densities. Under usual culture conditions their multiplication is stopped by the exhaustion of medium components, especially serum. Therefore, activation of fibroblastic cells that migrate from a dense layer into a wound is likely to be caused by their ability to utilise the medium more efficiently. Indeed, Stoker¹¹ has shown that there are important differences in the state of cells in a layer and of isolated cells as are found in a wound, in that isolated cells have better access to the medium. Probably the limitations in the layer are not affected by its density within a broad range.

In contrast, with epithelial cells a dish surface restriction is the predominant factor stopping growth; hence the increased availability of dish surface to the marginal cells after wounding may contribute to activate their growth. However, even for these cells it is unlikely that the dish surface requirement has to do with an inhibitory effect of contacts between cells. In fact, the epithelial cultures become resting long after the cells start touching each other; and when the cultures are wounded the cells at the edge of the wound do not become free from each other (except, perhaps, transiently during wounding) but migrate as a sheet, at the same time expanding their surface¹³.

Topoinhibition seems to result from different mechanisms in fibroblastic and epithelial cells; lower utilisation of medium components by cells in a layer in the former case, and a dish surface requirement (also perhaps with a decreased medium utilisation in the layer) in the latter case. The dish surface requirement may be an attribute of cells that must form a monolayer, as many epithelial cells do in nature in relation to their basal membrane. Fibroblastic cells need not form a monolayer either in nature or in cultures.

On the basis of the foregoing, we believe that there is no experimental support for the concept that "contact inhibition of growth" is responsible for cessation of growth in dense cultures.

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Role of Diffusion Boundary Layer in Contact Inhibition of Growth

M. G. P. STOKER

Imperial Cancer Research Fund Laboratories, Lincoln's Inn Fields, London WC2

Use of a miniature pump to produce a local increase in velocity of medium across the surface of confluent 3T3 cells stimulates growth which is limited to the region of high velocity. This indicates that growth is limited by a diffusion boundary layer close to the cell surface. The events at the edge of wounded cell layers (topoinhibition) can be explained by local variation in the fluid microenvironment rather than by alterations in contact between cells.

CONTACT inhibition of growth of cultured fibroblasts like contact inhibition of movement¹ has attracted much interest but the role of contact is still uncertain, and for this reason the alternative names density-dependent inhibition² and topoinhibition³ have been proposed. It is now acknowledged that the supply of medium⁴ and particularly serum⁵⁻⁷ plays an important part in this phenomenon. Nevertheless, it has been difficult on this basis alone to explain the very short-range topographical effects seen in wounded cultures, which have remained the strongest evidence that contact between adjacent cells plays a role in inhibition of growth in confluent cell layers.

When a strip of 3T3 cells is mechanically removed from a confluent non-growing monolayer, growth begins in those cells which migrate from the edge of the confluent sheet into the denuded area⁸, and in individual cells this can be correlated with loss of contact with neighbours⁹. Since the non-growing cells still in the confluent sheet and the growing cells in the wound are in the same medium only a few micrometers apart, it has seemed likely that the difference in growth is due to changes in the intimate relationship between cells, probably involving contact.

There is, however, an alternative explanation^{3,10}. This would suppose that the emigrating cells at the wound edge travel through and respond to a concentration gradient in the surrounding medium, affecting the availability of some substance critical for growth. At first sight it might appear that convective movement in the fluid should be sufficient to prevent the development of such a very localised gradient, but fluid movement is known to be reduced in the layer very close to the cell surface. A sufficient increase in the velocity of the fluid medium over a cell sheet might, however, perturb a local concentration gradient and alter the growth of the cells.

introduces a recirculating movement into the existing medium in the dish, in a narrow stream, 0.5 to 1 mm wide at velocities of up to about 100 mm s⁻¹. The pump (Fig. 1) consists of a glass capillary tube about 3 cm long and of 2 mm bore, narrowing to about 1 mm at the tip, which is lowered into the medium.

The other end of the tube is inserted directly or by a flexible connector tube into the opening in a hearing aid earpiece (Medresco OL575, Cosmocord Ltd, Waltham Cross, U.K.). The latter is attached to a variable transformer with an output of 2-3 V a.c. at 50 Hz. This causes oscillation in the medium in the capillary tube which is translated at the tip into a unidirectional outward flow. The jet of medium produced is a narrow stream which fans out about 5 mm from the tip of the capillary tube and then circulates slowly as shown in Fig. 1. It has not been possible to measure the velocity accurately with the current used, but it is more than 10 mm s⁻¹ in the centre of the stream with a theoretical maximum of 100 mm s⁻¹ calculated from the oscillatory excursion in the capillary tube. Close to the surface of the cell layer this is reduced to 2-4 mm s⁻¹. Away from the main stream, in the recirculation region, the velocity is reduced to 1-4 mm s⁻¹, and close to the cell layer in this region it is too slow to measure.

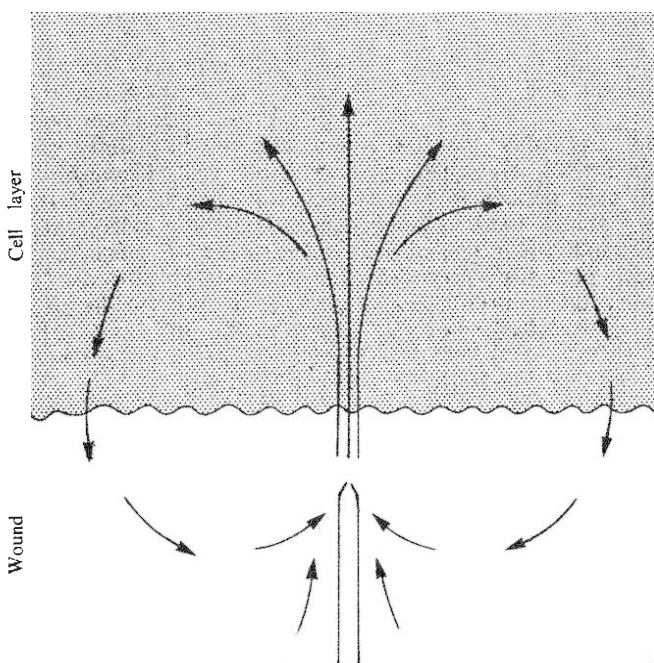


Fig. 1 Pattern of medium recirculation produced by pump across edge of cell sheet. Relative velocity indicated by length of arrows (not proportional).

Riddle's Pump

For this purpose I have used a small pump developed from an agglutination chamber designed by Riddle¹¹ which

Cultures of Balb 3T3 cells were grown to confluence in Dulbecco's modification of Eagle's medium with 10% foetal calf serum, and left without medium change for 4–7 d before use. The stationary sheets were wounded with a razor¹² and in most experiments fresh medium was added with 5% serum which is sufficient to stimulate growth in about 10% of cells in a confluent layer. The pump was directed across the edge of the wound towards the cell sheet with the tip of the denuded area about 2 mm from the edge of the cell layer and was allowed to run continuously while cultures were incubated in containers flushed with 10% CO₂. Controls were set up under identical conditions but with no pump.

Effect of Increased Velocity of Medium

When the cultures were examined after 26 h the number of mitoses and total cell numbers per unit area were seen to be increased in a small region of the cell sheet exposed to the fastest stream from the pump (Figs 2 and 3). A few millimetres from the main stream, even in the recirculating region the numbers of cells and mitoses were similar to those found in the rest of the dish and in the control unpumped culture. The mitotic index, which allows for the variation in cell numbers, was highest in the centre of the stream, 2.7% (19/700) compared to 0.5% (5/950) elsewhere in the dish.

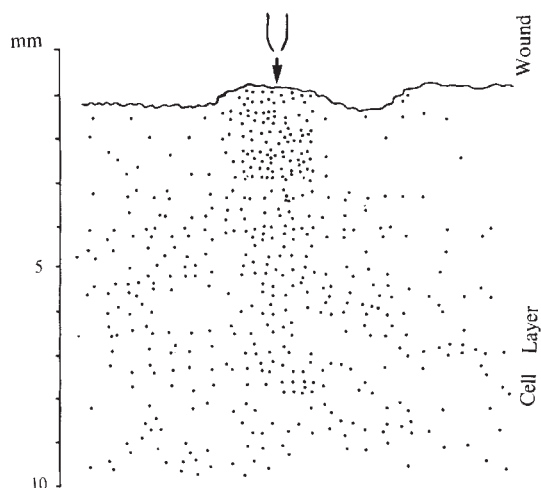


Fig. 2 Effect of local change in velocity of medium on distribution of mitoses. A strip of cells from a confluent stationary culture of 3T3 cells was removed with a razor, fresh medium with 5% calf serum was added, and the cultures incubated with the pump operating for 26 h, directed across the edge of the sheet. Each dot represents a mitosis at the distance shown from the pump.

After 22 h exposure to ³H-thymidine and subsequent autoradiography the distribution of labelled nuclei in the confluent sheet was similar to that shown for mitoses in Fig. 2. 76% of cells were labelled in the region of the jet compared to 10% elsewhere (at least 200 counted). In contrast 81% of cells emigrating into the wound were labelled irrespective of relationship to the jet.

Since cell density was increased and mitotic cells were not removed by the jet it seemed unlikely that the stimulation of growth was due to local reduction in cell density and contact caused by detachment of cells. This was confirmed by time lapse cinematography of the area in the stream, which showed no loss of cells. The film also showed that there was no displacement or distortion of cells in the direction of the medium flow. A temporary increase in local cell movement compared to unpumped cultures was seen which lasted up to 16 h. Since the movement stopped between 16 and 22 h, however, while the pump was still operating, it is unlikely

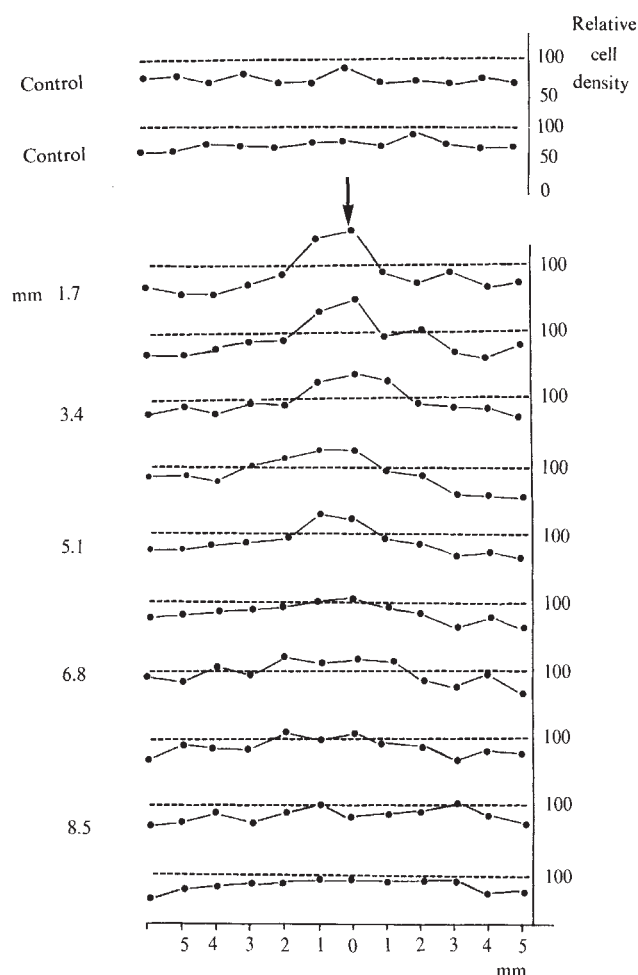


Fig. 3 Effect of local change in velocity of medium on cell numbers. Same culture as in Fig. 2. Cell numbers per unit area (0.15 square mm) are shown across the cell sheet parallel to the wound edge and at distances shown from the pump. Controls are (1) from the opposite side of the same layer (behind the pump) and (2) from a parallel but unpumped culture.

to be due to a direct physical effect of the fluid movement on the cells. It therefore seems likely that the stimulation of cell growth and movement with increase in velocity of the medium is due to concentration changes in the fluid micro-environment itself.

The Diffusion Boundary Layer

The behaviour of molecules in fluid close to a solid reactive surface has been extensively studied by physical chemists. Since the convective movement of most fluids approaches zero near a solid surface over which flow occurs, the transfer of molecules to and from the surface is largely limited to the relatively slow process of diffusion. This results in a diffusion boundary layer^{13,14} which can act as a barrier close to the reactive surface. If, for example, a cell rapidly removes a molecule essential for growth from the medium, the concentration near the cell surface will fall to a level determined by the uptake rate and the rate of replenishment by diffusion from the bulk of the medium. The supply of such a molecule may become limiting and the process (growth) then becomes diffusion controlled. The restriction can be relaxed by raising the concentration of the substance in the bulk medium, or alternatively by reducing the diffusion boundary layer. For a particular fluid the diffusion boundary layer is characteristic of each type of molecule and it is usually defined as the region with a concentration less than 90% of that in the bulk of the fluid¹³. Apart from the diffu-

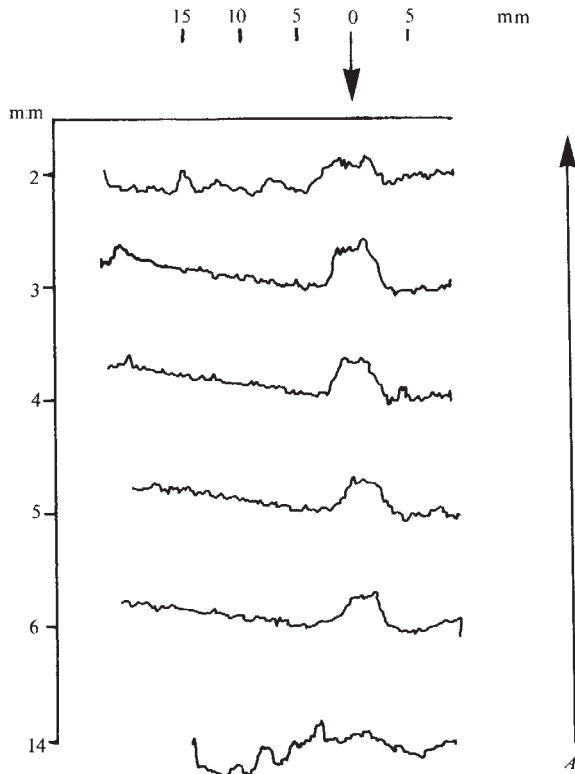


Fig. 4 Effect of local change of medium velocity on uptake of stain. A confluent layer of 3T3 cells was fixed and exposed to Giemsa stain (0.03%) with the pump operating. After 3 min, uptake of stain was measured by microdensitometer tracings at right angles to the fluid flow and at distances shown from the pump.

sion coefficient and the net loss to the reactive surface, which cannot be varied, the diffusion boundary layer is inversely proportional to the square root of the velocity of the medium flowing over the surface. The velocity can be increased and, as shown here, this does affect cell growth.

Effect of Velocity on Staining

The existence of a diffusion boundary layer, even over a fixed cell layer, may be demonstrated by the effect of velocity on uptake of a stain such as Giemsa stain. Staining of a confluent sheet of 3T3 cells may barely be detected after 3 min exposure to dilute Giemsa stain (0.03%). Use of the pump, however, to produce a local increase in fluid velocity over the sheet causes uptake of stain limited to the region of high velocity. Figure 4 shows microdensitometer tracings across a cell sheet at right angles to the fluid flow and at varying distances from the jet (see Fig. 3). It shows the increased absorbance due to higher stain uptake limited to the narrow band exposed to the stream of medium. By coincidence this corresponds topographically and therefore in velocity to the region of growth stimulation produced by the pump in living cell sheets. It does not follow, however, that a molecule limiting for growth is of a similar size to the methylene blue eosin in Giemsa, since the uptake rate may be different.

Growth in Wounded Cell Sheets

This investigation was carried out to find out if concentration changes in the medium over a wound could account for growth of cells migrating over a very short distance from the edge (of the order of one cell diameter). Assuming negligible uptake of a critical substance by the supporting plastic, there will be no diffusion boundary layer and no reduction in concentration of medium constituents over the denuded area

up to the edge of the cell sheet (or a single cell). At the wound edge, however, diffusion can occur laterally as well as vertically, so the boundary does not start abruptly. It increases in proportion to the square root of the distance from the edge of the sheet. This has been studied by chemists in the dye industry¹⁵, and even in fixed 3T3 cells uptake of Giemsa stain may be increased at the edge of a cell sheet compared to the rest of the sheet. It means that the concentration of a critical substance at the surface will be higher near the edge of a wound and then fall rapidly over the undisturbed layer as the diffusion barrier increases.

Since the critical substances themselves and many of the parameters are unknown, the shape of the resulting concentration gradient over the edge cannot be determined. If, however, the diffusion boundary layer becomes maximal over a distance of one or more cell diameters it will not be fully developed over isolated migrating cells or the single row of cells lining the edge, and the concentration of a limiting substance over such cells will not fall to the same level as that over the continuous sheet. Consequently, with limiting nutritional conditions, the growth of confluent cells would be restricted, while isolated cells which had migrated a short distance into the denuded area would be able to grow (Fig. 5a). A sufficient increase in the velocity of the medium would reduce the boundary layer and increase the concentration over the sheet (Fig. 5b).

It should be noted that an increase in velocity in any direction, not necessarily over a wound edge, will reduce the diffusion boundary layer. This has been confirmed by placing the pump over the cell sheet where it still stimulates

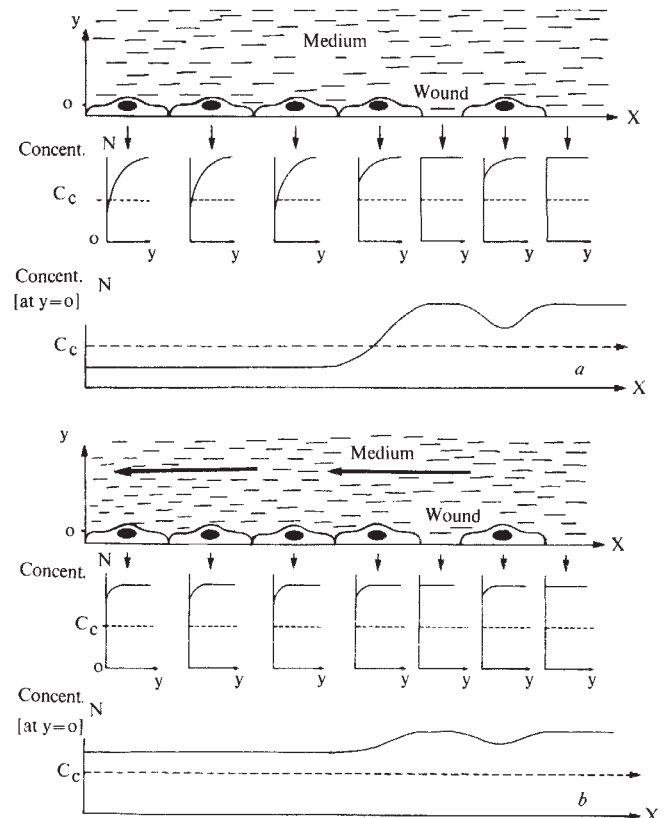


Fig. 5 a, Diagram showing changes in concentration of a hypothetical limiting nutrient across edge of a wound. Top part shows section of cell layer across wound with migrating cell on right, in stationary medium (convection only). Middle part shows concentration distribution vertical to cell sheet (y axis) over different regions. Lower part shows concentration distribution at the cell surface horizontally across the wound edge (x axis). C_c —concentration of hypothetical substance limiting for growth. b, Same as a but with increase in velocity of medium.

growth. When the medium flows towards the sheet from a denuded region without uptake of critical nutrients, however, the effect of the increased velocity is enhanced.

This paper emphasises the role of the diffusion boundary layer in limiting the uptake of critical nutrients or growth factors from the medium. The barrier could, however, operate in the opposite way, by preventing the escape of inhibitory molecules released by the cells. On present evidence the two mechanisms cannot be distinguished.

The original suggestion that a diffusion barrier could account for many of the effects of cell density was based on experiments with opposed cell layers made by Rubin and Rein¹⁰. My data support this view and show that concentration changes in the microenvironment could account for the highly localised growth of 3T3 cells at the edge of wounds and presumably also at the circumferences of colonies¹⁶. On this basis the reduction in density-dependent inhibition of growth, or topoinhibition, by virus transformation can be explained by a lowering of nutritional requirements. Even in those variants which show a lowered requirement for serum growth factor while remaining sensitive to topoinhibition¹⁷, another essential nutrient may be limiting.

It may be concluded that topoinhibition, as manifest at wound edges in 3T3 cells, is no longer evidence that contact between cells regulates their growth. The accompanying paper¹⁸ reaches the same conclusion on different grounds.

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LETTERS TO NATURE

PHYSICAL SCIENCES

A Double Quasistellar Object

BECAUSE QSOs are rare^{1,2} the discovery of close pairs with discordant redshifts is improbable if they are randomly distributed on the plane of the sky. But Stockton³ has reported that Ton155 and Ton156 form a pair of 17 mag QSOs, with a separation of approximately 35 arc s. For QSOs randomly distributed on the plane of the sky he gives the probability for an accidental occurrence of this close pair as 6×10^{-3} .

Visually, 1548+115=4C11.50 (ref. 4) is another close pair of blue stellar objects. The brighter object (1548+115a) is approximately 17 mag, and is followed 4.8 arc s east and 0.4 arc s south by the 19 mag object 1548+115b. The pair was first noted by Hazard and Jauncey (see ref. 5) in a programme of 4C identifications, and has also been noted by Murdoch and Hazard (unpublished) in a programme of identifications based on Molonglo radio positions. It had been found earlier⁴ that 1548+115b was a QSO although its redshift had not been determined nor had the nature of 1548+115a been established. We report here that 1548+115a is also a QSO and give additional spectral information for both objects. In particular we note the very different redshifts of the objects; $z=0.4359$ for 1548+115a and $z=1.901$ for 1548+115b. The radio source is a 3C273 type double (Ekers and Fanaroff, private communication) with one component coincident with 1548+115a. There is a faint red wisp of otherwise unknown characteristics visible on the National Geographic Mount Palomar Sky Survey plates ~10 arc s south-west of 1548+115a.

On the nights of August 1, 3–6, and 24–25, 1973 (UT), 1548+115a,b were observed optically with the Cassegrain scanner⁶ of the 120-inch (305-cm) telescope. At that time of year 1548+115 can only be observed early in the evening in the western sky. The astronomical seeing was generally good during the earlier observing period and small (~2 arc s) spectrograph entrance apertures were used to reduce the background illumination from the lights of nearby cities. On the nights of August 24–25 the conditions were much poorer and only 1548+115a was observed. The use of small apertures, especially in the presence of substantial atmospheric dispersion, prevented us from obtaining an accurate continuum flux calibration. For this reason we are uncertain of the spectral index of the continuum although the magnitude estimates obtained in August ($m_v=16.8$ and 18.8) are in good agreement with those obtained earlier⁴. Our best estimate for the spectral index of 1548+115a is $\alpha=0.8 \pm 0.5$ and for 1548+115b $\alpha=0.6 \pm 0.4$ where α is the index in the equation $f_\nu \sim \nu^{-\alpha}$. Because the objects are so close together scattered light is a potential problem, but measurements of the scattered light from a bright star set 5 arc s off the slit showed no significant effects.

Both objects show rich emission line spectra. The observed lines, their identifications, and equivalent widths are listed in Table 1. The adopted redshift for 1548+115a is $z=0.4359$ and for 1548+115b we adopt $z=1.901$. If both objects were at the cosmological distance corresponding to $z=0.4359$ their separation would be about 40 kpc ($H_0=50 \text{ km s}^{-1} \text{ Mpc}^{-1}$, $q_0=1/2$). Figure 1 shows the observed spectra of the two objects. They seem to be normal for QSOs. Also the objects seemed stellar in the television guiding monitor of the 120-inch telescope. If either object were discovered alone in the sky it

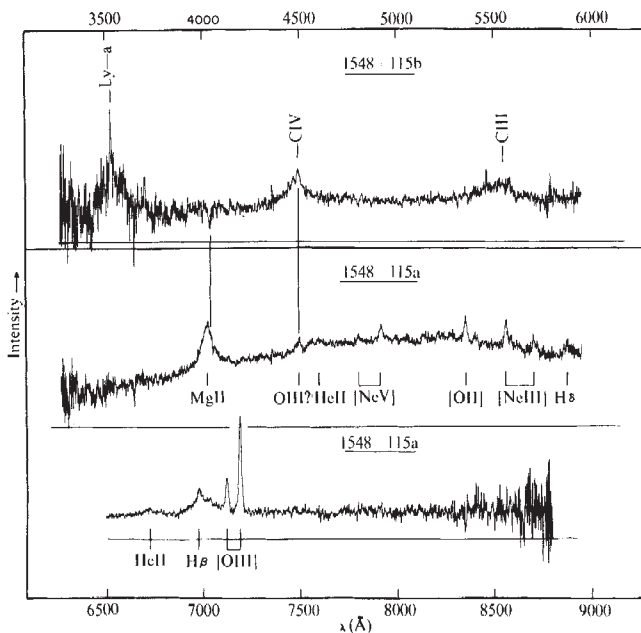


Fig. 1 Spectra of 1548+115a,b. Evidence of poor subtraction of the strong Hg night sky lines at $\lambda\lambda 3650, 4047$ may be seen in the spectra. But a close inspection of our data shows that the strong absorption feature seen at $\lambda 4038$ in the spectrum of 1548+115b is not caused by incorrect subtraction of Hg $\lambda 4047$. The two vertical lines show the correspondence between the $\lambda 4038$ and $\lambda 4495$ features in the spectra of 1548+115a,b.

would be classified as a normal QSO. In addition to the close proximity of the two objects to each other in the plane of the sky and the possible alignment of the optical and radio sources, there are several coincidences in the spectra of the two objects.

First, there is a strong absorption feature at $\lambda 4038$ in the spectrum of 1548+115b that lies slightly to the red of the redshifted Mg II $\lambda 2800$ emission peak in the spectrum of 1548+115a. The spectral data are not of high enough quality to decide conclusively if the feature is due to Mg^+ or to some other ion, such as C^{3+} . An accurate determination of the profile of the absorption line is hindered by the presence of a strong night sky line, Hg $\lambda 4047$, in the red wing of the feature. But we were able to use the night sky line to determine the instrumental profile and to construct artificial profiles representing doublets with separations corresponding to C^{3+} and Mg^+ . A comparison of these profiles with the observed profile is given in Fig. 2.

Table 1 Observed Lines in 1548+115a,b

Ion	Observed λ	1548+115a Rest wavelength	Equivalent width (Å)	z
Mg II	4024	2800	70	0.4382
O III ?	4496	—	4	—
He II*	—	3203	9	—
[Ne V]	4801	3346	2	0.4348
[Ne V]	4916	3426	5	0.4345
[O II]	5350	3727	5	0.4352
[Ne III]	5556	3869	6	0.4360
[Ne III]+He	5696	3968+3970	4	0.4350
Hδ	5880:	4102	13	0.4335:
He II*	—	4686	21	—
Hβ	6982	4861	91	0.4361
[O III]	7123	4959	18	0.4364
[O III]	7193	5007	62	0.4366
1548+115b				
Ly-α	3527	1216	224	1.901
Absorption	4038	—	12	—
C IV	4493	1549	83	1.901
C III]*	5555:	1909	65	1.910:

* Line not used to determine redshift.

Inspection shows that the absorption feature is probably due to C^{3+} .

Second, the presence of emission features close to $\lambda 4495$ in the spectra of both objects led to speculation that the C IV $\lambda_{\text{O}} 1549$ feature might be present in both objects at $z=1.901$. But the line of $\lambda 4496$ in the spectrum of 1548+115a is very probably a blend of the O III $\lambda 3122, \lambda 3133$ Bowen fluorescence lines⁷ in the $z=0.4359$ redshift system. The other lines in the O III cascade chain would be confused with the [Ne V] $\lambda 3346, \lambda 3426$ doublet and are possibly present at their expected strengths. Several other QSOs are known to have an emission line at a rest wavelength near $\lambda 3135$. Ly-α at $\lambda 3527$ does not appear in our spectrum of 1548+115a, a circumstance that strengthens the probability that the wavelength agreement between the $\lambda 4495$ features is accidental.

Finally, we note that the wavelength ratio $(1+z)_a/(1+z)_b = 2.02$. Although the observational data are sufficiently accurate to exclude the possibility that the true ratio as determined from the emission lines in the two objects is exactly 2, it would be possible for the departure from 2 to be caused by small peculiar motions associated with one or both of the objects. This difference of almost exactly a factor of two in wavelength for these two (optically) associated objects is either an unfortunate coincidence or a profound mystery.

The discovery of surprising objects such as this tempts us to make statistical arguments. Arguments about rare single events are treacherous; the archives of science are filled with dead hypotheses, supported initially by overwhelming statistical claims. One must avoid the errors of either testing only a single hypothesis, or of selecting an *ad hoc* alternative and then confirming it on the basis of the same data.

Before the observation of double QSOs, the 'most likely' hypothesis was the cosmological hypothesis: Redshifts were cosmological in origin, with a small component due to peculiar velocities. In general QSOs were expected to be randomly distributed on the plane of the sky and any groups that did appear should agree in redshift. Another hypothesis, less definite but existing before these observations, was the local

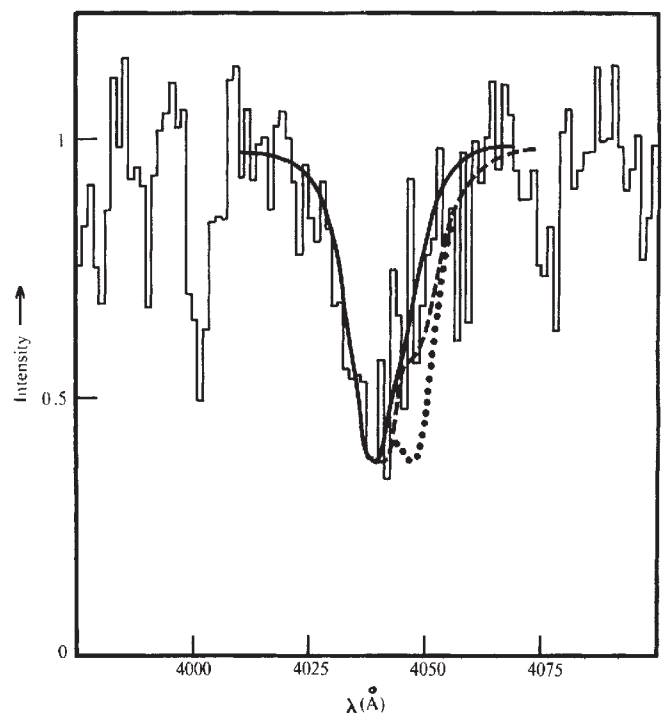


Fig. 2 The $\lambda 4038$ absorption feature in 1548+115b. The curves are computed instrumental profiles for: —, C IV $\lambda\lambda_{\text{O}} 1548.2, 1550.8$ with a 1:1 intensity ratio; ---, Mg II $\lambda\lambda_{\text{O}} 2795.5, 2802.7$ with a 2:1 intensity ratio; and . . . , Mg II $\lambda\lambda_{\text{O}} 2795.5, 2802.7$ with a 1:1 intensity ratio. The night sky line Hg $\lambda 4047$ increases the uncertainty in the red wing of the QSO absorption line.

hypothesis. The observed redshifts were allowed a large, non-cosmological, component and groups of QSOs could now have discordant redshifts.

Our observation of a close pair of QSOs with discordant redshifts is unlikely under the cosmological hypothesis. Sandage and Luyten¹ estimate that there are five QSOs brighter than magnitude 19.4 per square degree. If this is true and if QSOs are randomly distributed in the sky the chance of finding a second QSO within 5 arc s of a given object is approximately 4×10^{-5} . The probability of finding such a pair among the 250 QSOs with known redshifts is about 1 in 100 if there were no observation selection effects. Present observational techniques certainly discriminate against finding close doubles since normally the search is stopped when one candidate from a group of stars is found to be a QSO.

A local hypothesis which puts 10% of the QSOs in pairs of galactic cluster dimensions, say one minute of arc, is at a statistical advantage by a factor of thirty or so. The radio alignment, when accurately measured, may provide additional evidence. The spectral peculiarities are fascinating but no pre-existing theory suggested them and these observations only raise them for future consideration.

We believe that these observations add support to non-cosmological theories of redshifts. Such theories will receive additional support if an interaction between the two components of a close pair can be shown. Alternatively, additional close pairs may be found. Since it is now known that some large redshift QSOs have neutral colours⁸, a search for more QSO pairs should include all stars found near suspected or known QSOs.

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E. J. WAMPLER
J. A. BALDWIN
W. L. BURKE
L. B. ROBINSON

Lick Observatory, Board of Studies in
Astronomy and Astrophysics,
University of California, Santa Cruz

C. HAZARD

Institute of Astronomy,
University of Cambridge

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Discrepant Redshifts of QSOs in Clusters of Galaxies and a Close QSO Pair

ALTHOUGH it is the majority view that QSO redshifts are cosmological in origin and related to distance by Hubble's law, several workers¹⁻³ have proposed that QSOs may be more local objects. The strongest direct evidence for the conventional view is provided by observations of a number of QSOs which have been shown to have redshifts (z) which agree to within about 1% with the redshifts of apparently associated clusters of galaxies⁴⁻⁸. These QSO-cluster asso-

ciations have all been found in searches restricted to QSOs with $z < 0.36$ since on the cosmological hypothesis it is only for such low values of z that the associated galaxies would be readily visible. But, as Burbidge and O'Dell⁹ have pointed out, by assuming at the outset that the redshifts are cosmological these investigations fail to test the non-cosmological hypothesis. For the past several years we have been attempting to carry out a study of QSOs in clusters or groups which would be free from this objection. Although our results are by no means complete, we present here some of our preliminary findings as they seem to be of relevance to the present controversy.

To avoid any assumptions as to the nature of the redshifts, two of us (D. J. and C. H.) started, not with a list of QSOs, but with a list of 280 radio sources selected from the 4C catalogue and for which we had measured improved positions. The fields around each of these sources were examined on the Palomar Sky Survey Prints for possible QSO identifications, an identification being suggested whenever a blue stellar object (BSO) brighter than 19 mag was found within the error rectangle of the radio position¹⁰. In searching for possible associations with clusters we adopted the view that a QSO is typically brighter than the brightest cluster galaxies by up to 2 or 3 mag. We therefore noted all cases in which three or more galaxies lay within 1 (arc min)² of the suggested QSO identification and which on the Palomar Sky Survey E print were approximately equal to it in brightness. We noted QSOs with less than three nearby galaxies only if these were brighter than 19 mag and lay within 10 arc s. This approach not only differs from that adopted in other QSO-cluster investigations but also differs significantly from that of Burbidge *et al.*¹¹ who looked for an association between QSOs and much brighter galaxies. It assumes that the QSOs are at cosmologically significant distances rather than very local ones but not necessarily at distances given by Hubble's law.

A search was also made for situations in which more than one BSO lay close to the radio position, a few examples of this type having already been noted¹². It seemed possible that these might represent physical associations of QSOs the significance of which would be easier to establish than QSO-galaxy associations. They would therefore provide a more powerful method of investigating any possible non-cosmological contribution to the QSO redshifts, particularly if this non-cosmological component were present only in high redshift objects, say $z > 1$.

A BSO or possible BSO was found within the search area of fifty-three of the 280 sources examined. Of these fifty-three, two (4C04.54 and 4C28.40) were found to be within 1 arc min of a second BSO, three (4C24.23, 4C11.45 and 4C26.48) lay close to one or more galaxies and the sixth (4C11.50) showed both a close pair of BSOs and a galaxy within the error rectangle. The latter four cases were considered to represent the most probable associations and to be worthy of further study, the remaining forty-nine have been published elsewhere¹⁰. The adopted radio positions of the four selected sources and their position relative to the nearby BSOs are given in Table 1 and enlargements of the fields around each of the sources are shown in Fig. 1.

The most convincing case for a QSO-cluster association is provided by 4C24.23; the BSO is seen clearly near the edge of a small compact group of five galaxies which may represent the brightest members of a cluster extending over a diameter of about 2 arc min. The BSO is the brightest member of the group, consistent with it being a QSO at the same distance. The BSO identified with 4C11.45 is also the brightest member of a small compact group but both the galaxies and the BSO are some 2 mag fainter than in the case of 4C24.23. A line of three brighter galaxies within 2 arc min may be members of the same cluster. 4C26.48 and 4C11.50, each with only a single galaxy within 10 arc s, are less convincing. 4C11.50 was, however, also of par-

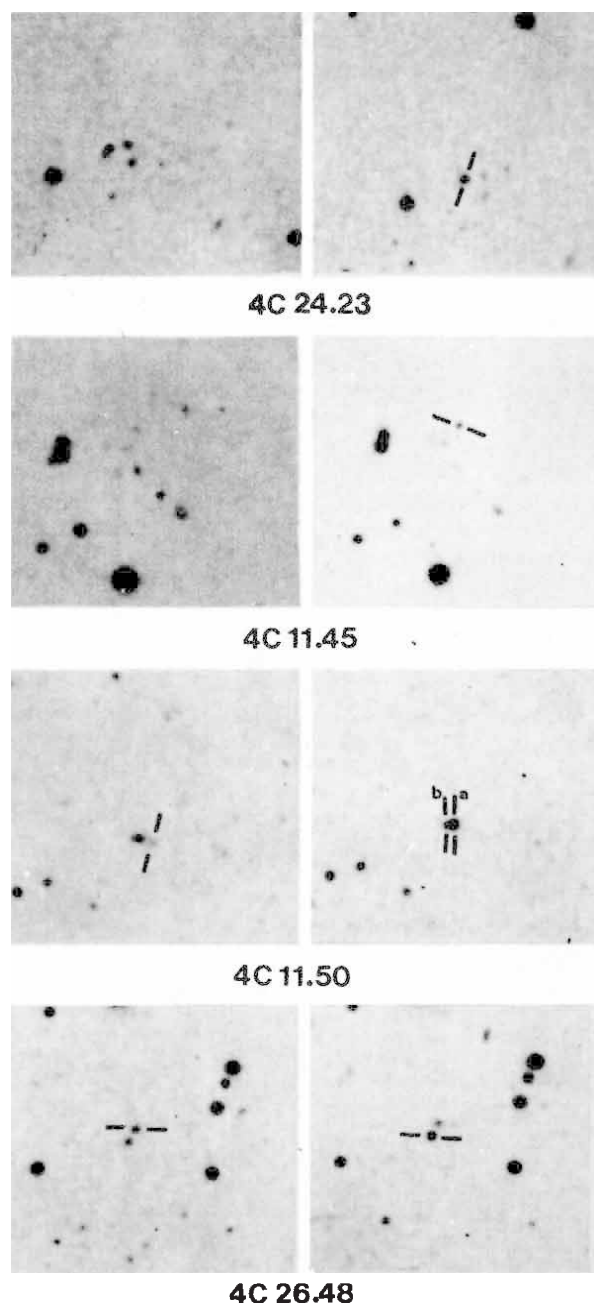


Fig. 1 Enlargements from the Palomar Sky Survey Prints of the region around the four sources, the E enlargement being on the left and the O enlargement on the right in each case. The quasistellar objects are marked on the O enlargements, and for 4C11.50 and 4C26.48 the nearby galaxies are marked on the E enlargement. Each picture is about 3 (arc min)^2 and north-east is at the top left hand corner.

ticular interest because of the presence of the two BSOs separated by only a few seconds of arc. The pair of BSOs can be clearly seen on the Palomar O plate although the fainter of the two is barely visible on the E plate which is of rather low quality. The galaxy which is visible only on the E plate is of comparable magnitude to this fainter BSO.

At this stage, because of the low accuracy of the radio positions, it was not certain that the BSOs we had noted were really QSOs rather than chance associations with blue stars. Nor could the possibility be excluded that one or more of them was a radio-quiet QSO with the radio emission originating in one of the nearby galaxies. A search of the literature showed, however, that 4C11.45 and 4C26.48 had already been suggested and confirmed as QSO identifications¹³⁻¹⁵. Since then we have taken optical spectra of

Table 1 Positions of the Four Radio Sources and the Relative Positions of the Optical Identification

Source	Adopted radio position (1950)						S_{430} f.u.	Relative position of optical identification	
	Right ascension			Declination				optical-radio "	"
	h	min	s	°	'	"			
4C24.23	10	48	46.8	24	04	18	(2.9)	0	18S
4C11.45	13	18	50.0	11	22	30	4.8	4P	5N
4C11.50	15	48	22.0	11	30	00	1.8	6P	12S
4C26.48	16	23	12.8	26	57	30	2.8	12P	12S

4C24.23 using the 200-inch telescope at Palomar and the two BSOs near 4C11.50 have been studied by Baldwin *et al.*¹⁶ at Lick Observatory. Both 4C24.23 and the fainter member of the 4C11.50 pair (4C11.50b) have been confirmed as QSOs and the brighter member of the pair (4C11.50a) was noted as having a continuum spectrum. In addition Ekers (private communication) has determined structures and accurate positions ($\pm 0.5 \text{ arc s}$) for all four radio sources using the Westerbork Aperture Synthesis array, and Fanaroff (private communication) has measured the structure of 4C11.50 using the Cambridge aperture synthesis instrument. Optical positions accurate to about $\pm 0.3 \text{ arc s}$ have been measured by Argue and by Murdoch (private communications).

A full account of these observations will be published elsewhere; at present we note that the accurate optical and radio positions confirm that for 4C24.23, 4C11.45 and 4C26.48 the radio emission does indeed originate in the QSO. The observations of 4C11.50 are particularly interesting since they show that the source is double with a separation of $\sim 15 \text{ arc s}$ in position angle 152° but with one component coincident with 4C11.50a rather than the confirmed QSO, 4C11.50b. This indicates that the source is a 3C273-type double and that 4C11.50a is also a QSO. The separation of the two QSOs is only 4.5 arc s so the possibility that they are physically associated inevitably arises. The nature of 4C11.50a has also been confirmed independently of these radio observations by Wampler *et al.*¹⁷ in a parallel optical investigation and redshifts have been measured for both it and 4C11.50b. A summary of the relevant optical information is given in Table 2.

Although the redshifts of none of the galaxies close to any of the four QSOs have been measured, we estimate from their magnitudes that they cannot in any case exceed a value of approximately 0.3. It can be seen from Table 2 that, apart from 4C11.50b, the QSO redshifts exceed this value of z to such an extent that they cannot be associated with the galaxies if the redshifts of QSOs and galaxies are both distance indicators. The possibility remains, however, that the

Table 2 Optical Data in the Suggested QSO Galaxy Association

Source	QSO magni- tude	Redshift	Notes
4C24.23	18.5	1.27	QSO in small group of galaxies
4C11.45	19	2.17 (ref. 15)	QSO in faint cluster of galaxies *
4C11.50 (a)	17†	0.43 (ref. 17)	Close pair of QSOs. 19 mag galaxy $10''$ preceding
(b)	18.5	1.90 (ref. 17)	
4C26.48	17.5	0.78†	18 mag galaxy $10''$ north pre- ceding

* Clarke, Bolton and Shimmins¹³ have previously noted this cluster.

† The identification of 4C11.50a as a QSO has already been made by Wills and Bolton¹⁸, but neither the second QSO nor the galaxy was noted. The group of three objects has also recently been noted by Murdoch and Hazard (to be published) in an identification programme based on Molonglo radio positions.

‡ Provisional value communicated by M. Schmidt.

Table 3 Results of Counts

No. of galaxies	0	1	2	3	4	5	6	7	8	9	10
No. of (a) regions in which observed	178	90	28	1	2	1	1	0	0	0	0
No. of (b) regions in which observed	54	79	69	49	24	13	5	1	3	2	1
No. of (c) regions in which observed	22	38	40	22	6	1	0	1	0	0	0

associations are genuine but that the redshifts are not distance indicators. To support this view it would be necessary to obtain very strong evidence to rule out chance associations. In the absence of evidence showing radio or optical links to the nearby galaxies the only evidence which can be provided must be based on counts of galaxies and clusters of galaxies.

As it has been shown that the radio emission in all four examples arises in the QSO and not in the galaxies or clusters of galaxies, we need to know only the probability that out of the chosen sample of 280 radio sources four quasistellar radio sources will be found in the observed configurations; the probability of a radio-quiet QSO lying close to a galaxy need not be considered. Out of the 280 radio sources, fifty-three were suggested as possibly associated with QSOs with probably 30% representing chance coincidences with blue stars. This indicates that we are dealing with a list containing about forty QSOs which is consistent with the percentage of QSOs (~15%) usually found in source lists at the flux level of the 4C survey. The probability of two cases of a single galaxy being observed within 10 arc s of a QSO is then easily estimated from the published galaxy counts. Counts by Hoskins *et al.*¹⁹ give the probability of a galaxy above +19 mag occurring by chance within 10 arc s of a randomly chosen position as about 0.02 and hence the probability of observing two such cases in a sample of forty QSOs is about 0.3. This ignores the restriction placed on the initial survey of noting only galaxies close to QSOs when they were of comparable magnitude on the Palomar E plate. Even if this were taken into account, however, the probability could not be reduced to a significant level.

The probability that the remaining two QSOs would be observed by chance in small groups of galaxies is more difficult to assess as no figures are available for the surface density of such groups, and in any case the definition of a group is to a large extent subjective. To provide some estimate we have counted the number of galaxies seen above the plate limits in 300 randomly selected regions of sky (a) for 1 (arc min)² centred on each of the chosen points; (b) for 4 (arc min)² centred again on the chosen point; and (c) for 130 such regions we have counted the maximum of galaxies which were observed in any 1 (arc min)² not centred on the chosen point but still containing it. The results of these counts are shown in Table 3. The corresponding number of galaxies observed around 4C24.23 and 4C11.45 is shown in Table 4.

Similar numbers of galaxies would be observed by chance in about one trial in a hundred. In our random counts in most cases where the number of galaxies counted exceeded five per area, they were all at the plate limits, and with our selection criteria would not have been considered as clusters at the same distance as at least the brighter BSOs. A probability of 0.01 is therefore a conservative estimate of the chance of finding a QSO in small groups of the type we

have noted. Adopting this estimate we then find that the probability of finding two such cases in our sample is about 0.08. If the redshifts of the QSOs associated with 4C24.23 and 4C11.45 lay in the region of 0.1 to 0.3, even this probability would have led us to believe that we were dealing with physical associations and that the QSO redshifts are indeed distance indicators.

The probability is, however, too high by some orders of magnitude for our results to lend much support to the non-cosmological hypothesis. Therefore, although the possibility that the associations are genuine cannot be ruled out, the realistic interpretation is that we have simply chance associations of QSOs with small clusters of galaxies. We point out, however, that in their appearance on the Sky Survey Plates, 4C24.23 and 4C11.45 appear at least as convincing QSO-galaxy associations as those which have been used to support the cosmological hypothesis. That the only QSO-galaxy associations suggested prior to a redshift measurement should show discrepant redshifts is at least of some interest, if only to demonstrate that all possible associations do not necessarily support the conventional view.

An examination of the figures of galaxy counts presented here shows that it will be extremely difficult to establish a non-cosmological contribution to the QSO redshifts on the basis of an association with clusters of galaxies unless additional information can be obtained to rule out the possibility of chance associations. The detection near 4C11.50 of a possibly physically associated pair of QSOs seems, however, to offer a more promising approach. Assuming that these are 10⁵ radio-quiet QSOs in the sky brighter than +19 mag (ref. 20), the probability of detecting one within 5 arc s of a quasistellar radio source in a sample of forty such objects is only of the order of 6 × 10⁻⁴. In spite of their different redshifts the probability that we are dealing with a real association is therefore high, particularly as Stockton²¹ has already reported two radio-quiet QSOs separated by only 35 arc s, and which he estimates have a probability of occurring by chance of only 6 × 10⁻³. To establish beyond doubt the existence of associations of QSOs will require many more examples, preferably with more than two members, and it is to be hoped that the examples of two or more blue objects close to the position of a radio source which have already been reported^{12,13} will now be investigated optically. It may be that a significant test of the nature of QSO redshifts is at last in sight. A detailed account of the optical observations of 4C11.50 and their significance is given elsewhere by Wampler *et al.*¹⁷

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C. HAZARD

*Institute of Astronomy,
Cambridge CB3 0HA*

D. L. JAUNCEY

*National Astronomy and Ionosphere Center
and Cornell-Sydney University Astronomy
Center,
Cornell University, Ithaca, New York*

W. L. W. SARGENT

*Hale Observatories,
California Institute of Technology,
Carnegie Institute of Washington*

J. A. BALDWIN
E. J. WAMPLER

*Lick Observatory,
Board of Studies in Astronomy and
Astrophysics,
University of California,
Santa Cruz*

Table 4 Number of Galaxies around 4C24.23 and 4C11.45

No. of galaxies in region	(a)	(b)	(c)
4C24.23	4	10	6
4C11.45	5	8	6

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Force on a Wire in a Magnetic Field

McCAIG¹ has suggested that a shape factor might be involved in determining the force on a current-carrying wire in a magnetic field when there is a permeability contrast between the wire and its surroundings.

Certainly, the $\mathbf{B}$ seen by the conduction electrons in the wire would then be different from that present before the wire was inserted, apparently leading to a force which depended on the wire shape and permeability as well as the current, but this then gives difficulties when considering the mutual force between two different wires carrying the same current.

The problem of the cylindrical wire with uniform current density has in fact been solved by Stratton (ref. 2, section 4.21); a simple solution of the more general two-dimensional problem is now presented and discussed. I shall show that there is no shape factor for the force in the general two-dimensional case or for an arbitrary complete circuit. There is, however, a shape factor for the torque.

For simplicity let us consider a two-dimensional equilibrium situation with all quantities independent of z , that is, a long straight wire in a transverse field. We wish to calculate the force per unit length required to hold the wire stationary.

The external medium is assumed to be an incompressible fluid; it is homogeneous, isotropic and linear, and has relative permeability μ_e .

Before the wire is inserted there exists a uniform field

$$\mathbf{B}_0 = \mu_e \mu_0 \mathbf{H}_0 = \mu_e \mu_0 H_0 \hat{\mathbf{x}}$$

The medium is of sufficient extent, and the field sources sufficiently distant, that the insertion of the wire does not significantly alter the reluctance seen by the sources. Nor are the sources affected by the field of the current.

The long straight wire carries a current $I_0 = I_0 \hat{\mathbf{z}}$. The wire can have arbitrary mechanical and electrical properties, arbitrary cross-section, and arbitrary current distribution across it, provided all these are independent of z .

The field produced by the current will in general not be circular, and inserting the wire into the field will also distort $\mathbf{H}_0$. Outside the wire the total field $\mathbf{H}$ (strictly $\mathbf{B}/\mu_e \mu_0$) can be expressed in terms of a vector potential

$$\mathbf{H} = \text{curl}[\mathbf{T}(\rho, \lambda) \hat{\mathbf{z}}]$$

with

$$\nabla^2 T = 0.$$

The appropriate solution for T is

$$T = H_0 y + a_0 \ln(1/\rho) + \sum_{n=1}^{\infty} \rho^{-n} (a_n \cos n\lambda + b_n \sin n\lambda)$$

corresponding to $H_0 \hat{\mathbf{x}}$, a circular field $a_0 \hat{\lambda}/\rho$, and line dipole, quadrupole (and so on) fields proportional to a_n/ρ^{n+1} . Only the circular field contributes to $\oint \mathbf{H} \cdot d\mathbf{l}$ taken round a circle, so $a_0 = I_0/2\pi$, independent of the choice of origin.

The force of electromagnetic origin acting on the wire will come from both body forces (magnetic forces on the current and on the magnetisation) and surface forces (non-uniform pressure of the surrounding fluid). Fortunately it is the total force which is given by integrating the Maxwell stress over any surface surrounding the wire and entirely in the fluid (ref. 2, section 2.29):

$$\mathbf{F} = \mu_e \mu_0 \int [(\mathbf{H} \cdot \hat{\mathbf{n}})\mathbf{H} - (1/2)H^2 \hat{\mathbf{n}}] dS$$

where $\mathbf{H}$ is the total field.

Let us make the integration surface the cylinder $\rho = a$. (It is easily shown that the ends do not contribute.) In equilibrium the force cannot depend on the radius of this surface, so the only non-zero contribution to the integral must come from the interaction of the uniform field $\mathbf{H}_0$ with the circular field $\mathbf{H}_1 = I_0 \hat{\phi}/2\pi\rho$. Keeping only these terms, and remembering $\mathbf{H}_1 \cdot \hat{\mathbf{n}} = 0$, it follows that

$$\mathbf{F} = \mu_e \mu_0 \int [(\mathbf{H}_0 \cdot \hat{\mathbf{n}})\mathbf{H}_1 - (\mathbf{H}_0 \cdot \mathbf{H}_1)\hat{\mathbf{n}}] dS$$

Performing the integration we find the force per unit length to be

$$\mathbf{f} = I_0 \mu_e \mu_0 H_0 \hat{\mathbf{y}} = I_0 B_0 \hat{\mathbf{y}} = \mathbf{I}_0 \times \mathbf{B}_0$$

Thus the force on the wire depends only on the total current it carries, and on the value of the uniform $\mathbf{B}_0$ present before the wire was inserted; it is independent of the shape and material of the wire, and the distribution of current in it.

Therefore the total electromagnetic force per unit length of the long straight wire is simply $\mathbf{I}_0 \times \mathbf{B}_0$. Unfortunately it does not seem possible to give a simple interpretation of this overall result in terms of the various forces acting on the wire.

To indicate the complexity of the problem, consider the much simpler situation when there is no $\mathbf{B}_0$, but only the current $\mathbf{I}_0$. One can see physically that provided the fluid has uniform permeability, and (effectively) extends to infinity, there is no reason for there to be any net force on the wire. That the net force is zero is confirmed very quickly by the Maxwell stress argument used above. However, let us consider the individual forces.

There will be induced magnetisation $\mathbf{M}(\rho, \lambda)$ in the fluid and in the material of the wire. The total field $\mathbf{B}(\rho, \lambda)$ can be expressed as $\mathbf{B} = \mathbf{B}_I + \mathbf{B}_1 + \mathbf{B}_e$, where $\mathbf{B}_I$ is that field which would be given by the current I_0 in free space, $\mathbf{B}_1$ that from the (internal) wire magnetisation, and $\mathbf{B}_e$ that from the (external) fluid magnetisation.

The resultant body force on the wire will come not only from the integral of the Lorentz force $\mathbf{j}_0 \times \mathbf{B}$, but also from the integral of the force $(\mathbf{M} \cdot \nabla)\mathbf{B}$ exerted on the wire magnetisation by the gradient of $\mathbf{B}$. Many of the contributions must cancel on integration, because they correspond to the 'action' and 'reaction' of forces between different parts and properties of the wire, but two terms are left. These are the volume integrals of $\mathbf{j}_0 \times \mathbf{B}_e$ and $(\mathbf{M} \cdot \nabla)\mathbf{B}_e$, both involving the field whose source is the (non-uniform) magnetisation of the surrounding fluid.

In addition to these body forces there will also be a surface force given by the integration of the (non-uniform, non-

isotropic) fluid pressure of magnetic origin; this third term also derives from the non-uniform magnetisation of the fluid. (Any hydrostatic pressure of gravitational origin will, for our incompressible fluid, be unaffected by the presence or absence of magnetic fields.)

The total force is, however, zero. Therefore either the integrated effects of the three terms are individually zero or the three effects are non-zero but cancel. That the forces are individually zero is reasonable for simple geometries but most unlikely for arbitrary geometry, so, even in this apparently simple situation, in general there must be a complicated balance between the body forces and surface forces which arise from the magnetisation of the fluid.

In the more general case with a B_0 there must be an even more complicated partial balance between the three types of force ($\mathbf{j} \times \mathbf{B}$, $(\mathbf{M} \cdot \nabla)\mathbf{B}$, and surface pressure), and one can only be thankful that the Maxwell stress approach avoids the need to calculate them individually.

The net result is, however, that, in this two-dimensional situation in a given fluid, long straight wires of whatever material or cross section carrying the same current experience the same force; there is no need for a shape factor, as suggested by McCaig¹. (He was, however, correct in suggesting that the solution to his problem might lie (partly) in pressure surface forces.) (If B_0 is in fact produced by, say, a parallel wire in a different medium, then the forces on the two wires are not equal and opposite, but the difference is the force required to keep stationary the boundary between the two media.)

Whatever the details of the force balance which leads to this simple result in the two-dimensional case, there is no guarantee that the same balance will hold in more complicated geometries. Nor can the Maxwell stress approach then be used, because it is no longer possible to integrate over a surface (effectively) entirely in the fluid. The force on a complete circuit can, however, be determined.

In fact there is no net force on a complete circuit in a uniform B_0 . (This can be seen by integrating the Maxwell stress over a spherical surface enclosing the circuit; by the same type of argument as used above, the only type of field of internal origin which can give a non-zero force by interaction with the uniform B_0 is that of a monopole.) We can therefore say that the two-dimensional result that the force on a wire does not contain a shape factor is valid also for the (zero) force on a complete circuit.

Although plausible, it has not been shown that the result holds for any portion of a circuit.

Although the force on a straight wire or complete circuit has been shown to be independent of shape and of permeability contrast, this is not true for the torque. Even in the two-dimensional case, any line-dipole field produced by the wire will give a torque; although the current itself cannot directly produce such a field it can induce a net line-dipole moment in any asymmetric permeability contrast.

In the more general situation of a complete circuit this contribution to the torque still exists, but there will now be other, probably larger, contributions. Consider, for example, a rectangular coil; the wire on one side of the coil will be magnetised by the field of the current in the opposite side, and will give an additional dipole moment, and hence torque, which will depend on the permeability contrast between the wire and the fluid.

McCaig's discussion was prompted by the experiment of Whitworth and Stopes-Roe³. They adjusted the current in a coil until the torque on the coil balanced the torque on a permanent magnet fastened to the coil, when both were immersed first in water and then in a paramagnetic fluid. In fact a rough estimate shows that the above effect would reduce the current change by about 5%.

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F. J. LOWES

School of Physics,
The University of Newcastle upon Tyne

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Evidence for the Opening of the South Atlantic in the Early Cretaceous

ONE of the cornerstones of continental drift is the fit¹ of the continental edges of Africa and South America by removal of the South Atlantic Ocean, which is thought to have formed by the rifting of these two continents some time in the Mesozoic and their subsequent drifting apart. We shall present evidence from marine magnetic anomalies in the southern South Atlantic that demonstrates that this initial rift first occurred in the early Cretaceous, probably in the Valanginian (~125 to 130 m.y. BP). This conclusion is based mainly on a magnetic lineation pattern that lies in the Cape Basin directly south-west of the continental edge of South Africa, although we very tentatively identify a few of the same anomalies on the other side of the ridge in the Argentine Basin.

West of Cape Town, South Africa, in the Cape Basin, there occurs a sequence of north-west trending magnetic anomalies which indicates that seafloor spreading took place from 130 to 110 m.y. BP (Fig. 1). In the Argentine Basin, possible correlative anomalies are identified, though their definition in the Argentine Basin is poorer than in the Cape Basin. As can be seen in Fig. 1, the anomalies (which we will call the Cape sequence) can be traced in the Cape Basin from 34° S to 40° S. A lack of properly oriented track lines prevents identification further south. Track lines immediately to the north of 34° S, though properly oriented, do not show the anomalies.

To the west of the lineated anomalies, the magnetic field is characterised by irregular, low amplitude anomalies which do not correlate from track to track. One has to go west to 4° E before encountering the lineated anomalies of the late Creta-

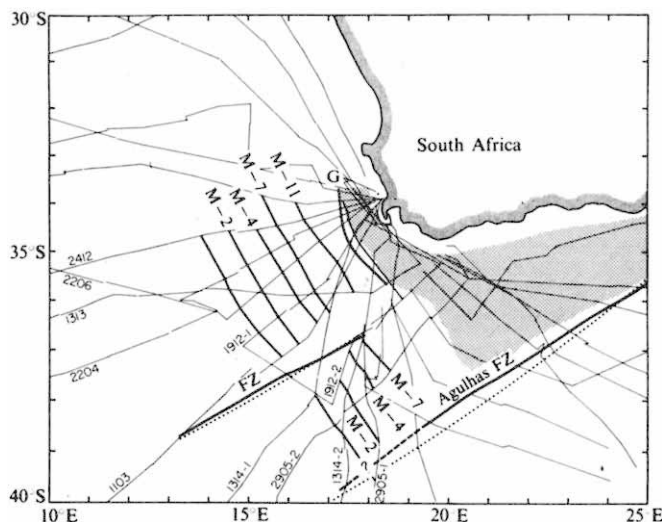


Fig. 1 Magnetic lineation chart of the Cape Basin off South Africa. Mesozoic magnetic lineations are labelled M. Lineation labelled G is the edge of the African continent defined by a steep gravity gradient by Talwani and Eldholm². The stippled pattern is an area of very small magnetic anomalies that corresponds to the submarine portion of the African continent³. Mapped fracture zones are shown with bold, solid or dashed lines. Synthetic fracture zones drawn as small circles about the pole of early opening³ are shown with dotted lines. Ship tracks are thin, solid lines. Magnetic anomaly data collected on the numbered ship tracks are shown in Fig. 2.

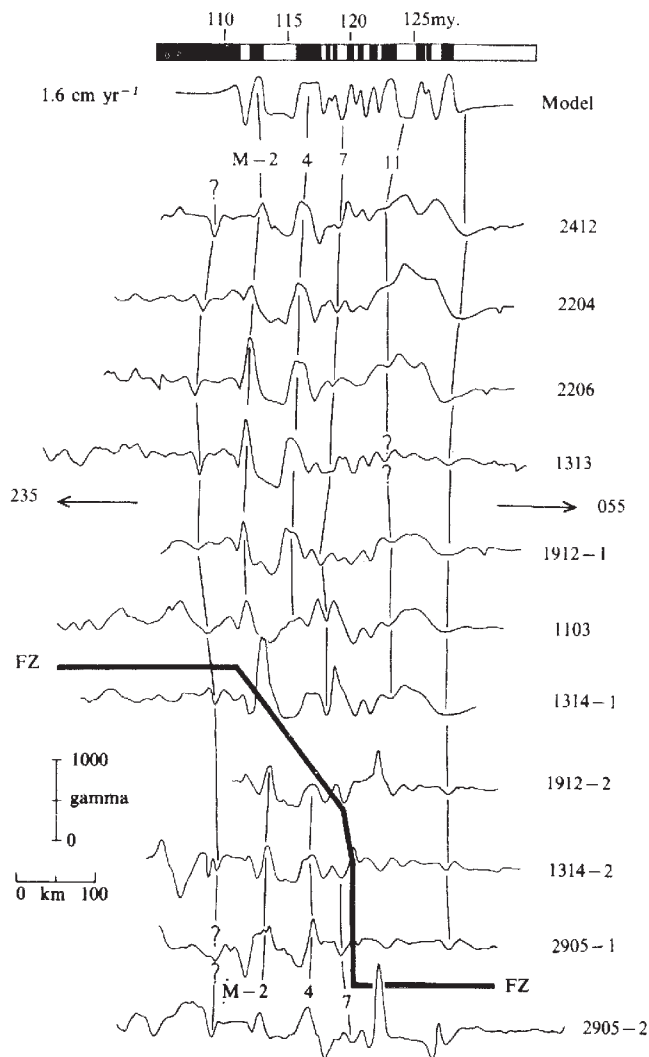


Fig. 2 Magnetic anomaly profiles across the Cape Basin lineations shown projected to a direction perpendicular to the structure. FZ is the small fracture zone offset shown also in Fig. 1. M lineations are from Larson and Pitman⁵. The magnetic block model was made by combining the Mesozoic reversal time scale⁵ with a spreading half rate of 1.6 cm yr⁻¹. The direction of remanent magnetisation is inclination=60° up, declination=30° W, in accord with a palaeomagnetic pole location for Mesozoic Africa at 65° S, 82° E (ref. 6).

ceous-Cainozoic reversal sequence which cover the mid-ocean ridge. Northward the Cape sequence trends into the marginal smooth zone defined² on the basis of aeromagnetic data. In the area of the Cape sequence, the aeromagnetic data reveal a sequence similar to that derived from the ship data used here. We do not show aeromagnetic data because the positions of magnetic anomalies so determined are offset several miles with respect to ours, and thus we suspect that the aircraft navigation is slightly in error.

To the east, the Cape sequence borders the continental margin as defined by Talwani and Eldholm³ using gravity and magnetic data. They suggested that the boundary between oceanic crust and continental crust is marked by a steep gradient in the isostatic gravity anomaly that lies at the edge of the continental structure. This gradient is nearly coincident with a change in the magnetic signature from a smooth, almost featureless magnetic field over the continental shelf and upper slope seaward to a region characterised by relatively large amplitude anomalies similar in magnitude and width to recognised seafloor spreading anomalies. It is these anomalies seaward of the upper continental slope that we have correlated with early Cretaceous anomalies recognised in the North Atlantic and North Pacific^{4,5}.

The correlations can be seen in Fig. 2 where the magnetic data were projected from several ship tracks on to a line trending N 55° E. At the top of Fig. 2 is a model computed using the Mesozoic reversal sequence⁵ determined by correlating the Mesozoic lineations in the North Pacific with the Keathley sequence in the North Atlantic. A mean Mesozoic palaeomagnetic pole at 65° S, 82° E (ref. 6) was used to determine the remanent magnetic direction for the model.

We consider the correlations, both from track to track and with the model, of anomalies M-1 to M-5 to be excellent. Note especially the well developed and well reproduced shapes of anomalies M-3 and M-4 and the spacing of anomalies M-2, 3 and 4. Anomalies M-6 and M-7 are usually present as modelled, but the lineation of the anomalies older than M-7 and their comparison with the model is often poor. We attribute at least some of this poorer correlation to disruption of the lineation pattern by the initial rifting phenomenon and point out that our identification of these anomalies as an expression of the Mesozoic reversal pattern rests almost wholly on evidence from the younger portion of the sequence. The oldest anomaly (Fig. 2) next to the continental edge is a well lineated negative feature that could be M-13, or the edge of the African continent³. Our model shows it as a reversal, but a non-magnetic (continental) block at this point would not change the shape appreciably.

The most disturbing part of this interpretation is the negative magnetic lineation that always occurs to the west of (younger than) anomaly M-1 (Fig. 2). This anomaly does not consistently occur in this position with respect to other Mesozoic lineation sequences^{4,5} although three negative lineations have been correlated⁷ east of (younger than) the Keathley sequence that may be related to the Bermuda Discontinuity. If our interpretation of these lineations in the Cape Basin as Mesozoic magnetic anomalies proves correct, it will be necessary to introduce another reversal into the magnetic time scale that is just younger than M-1.

A slight offset in anomalies M-1 to M-7 south of line 1314-1 indicates a fracture zone. On checking the seismic reflection profiler records, we were able to find additional evidence of a fracture zone in the area suggested by the magnetic lineations. The fracture zone shows up as discontinuities in basement topography, particularly as basement peaks. The peaks appear in the magnetic data as large, isolated, positive anomalies on tracks 1103 and 1314-1. This fracture zone parallels the Agulhas Fracture Zone^{3,8} to the south that appears in magnetic data as a large positive peak that parallels the south-east edge of the Agulhas plateau. In Fig. 1 we have drawn for comparison synthetic fracture zones about the early opening pole based on fracture zones in the central Atlantic⁹. The trends of the synthetic fracture zones are nearly identical to the trends of the two observed fracture zones. The fact that the trends of these fracture zones match the synthetic trends is additional evidence that offsets and lineations of the continental margins have recorded the directions of motion during the early opening⁹. In particular, the Agulhas Fracture Zone is the African counterpart of the Falkland Plateau scarp, a conclusion that was reached more qualitatively by observation of the trend of the south-eastern edge of the African continent by Francheteau and Le Pichon¹⁰, and by observation of a buried marginal ridge on the south-east side of the Agulhas Plateau by Scrutton and du Plessis⁸.

In the western Argentine Basin magnetic anomalies for the most part are subdued and display no coherence from track to track; however, four tracks from the Lamont data library over the lower continental rise off Argentina display two large positive anomalies that are consistent from track to track. There also seems to be a left lateral offset in the anomaly lineation pattern. The spacing is similar to anomalies M-2 to M-4 of the Cape sequence. Also, they are at about the same latitude relative to the pole of rotation as the Cape sequence, lie about the same angular distance from the continental slope as M-2 to M-4 in the Cape Basin, and their spacing shows the

same half-spreading rate. The above observations taken together indicate that some of the Mesozoic anomalies of the Cape sequence are also present in the Argentine Basin. We do not understand why they are not as well developed in the Argentine Basin. Model studies indicate that the greater depth to basement (~ 8 km) in the Argentine Basin will not attenuate the anomalies as much as observed.

Assuming that our anomaly identifications in both the Cape Basin and the Argentine Basin are correct and accepting the Talwani and Eldholm³ analysis of the continental margin west of Cape Town, a consistent picture is obtained by drawing the ocean basin and continents as they were at the time of formation of anomaly M-2. If the ocean is closed completely using the rotation to the 500-fathom line, a large (~ 100 km) gap is left open west of Cape Town. The extension of the African continent westward of the 500 fathom line as suggested by Talwani and Eldholm³ partially fills this gap.

Using the early opening pole⁹, we rotated anomaly M-2 of the Cape sequence back to the continental edge as defined by Talwani and Eldholm³. An angle of 2.3° is necessary for this rotation. This angle will represent half the motion of South America with respect to Africa between the initial rift and anomaly M-2. If South America, together with anomaly M-2 from the Argentine Basin, is rotated westward from the 500-fathom fit to Africa¹ by 4.6° (twice 2.3°) about the early opening pole⁹, the anomalies M-2 of the Argentine Basin nearly coincide with anomalies M-2 of the Cape Basin (Fig. 3). It is also apparent (Fig. 3) that the proposed left-lateral offset in the Argentine Basin then corresponds in position, sense and amount of offset with the small fracture zone that we identify in the Cape Basin.

Thus, our identification of the Mesozoic anomalies on both sides of the South Atlantic, Talwani and Edlholm's³ definition of the edge of the continent west of South Africa, and the 500-fathom average fit of the entire South American and African margins¹ are internally consistent. This suggests that the 500-fathom line may be a good average definition of the edge of the continent though locally (in the Cape Basin) there are deviations from this average.

Larson and Pitman⁵ did not recognise these Mesozoic magnetic lineations in the Cape and Argentine Basins and thus suggested that the South Atlantic did not begin to open until, or subsequent to, 110 m.y. BP. Our identification of these anomalies corrects this suggestion, but does not appreciably change their calculation of the rate of rapid spreading in the South Atlantic from 85 to 110 m.y. BP. It seems to lower the rate for that period by about 10%; for instance, at 40° S latitude the rate drops from about 5 to about 4.5 cm yr^{-1} . For the time period 110 to 127 m.y. BP the spreading rate is 1.6 cm yr^{-1} (see Fig. 2).

Figure 3 shows a reconstruction of Africa and South America at 112 m.y. BP (anomaly M-2 time) accomplished by the rotations just described. The relative proximity of the pole of rotation (21° N, 14° W)⁹ resulted in the early opening up to at least 112 m.y. BP occurring somewhat as a scissors-type motion. The lineations in the southern South Atlantic were generated in accord with motion at that latitude, while the northern South Atlantic remained more nearly closed. The close proximity of northern South America to northern Africa until at least 110 m.y. BP is in accord with palaeontological and stratigraphical studies in Brazil and Gabon that show freshwater lake deposits near or at the rifted coastlines throughout the Neocomian (~ 135 to 112 m.y. BP)^{11,12}. These were followed in the Aptian (~ 112 to 105 m.y. BP) by salt deposits in the same approximate locations^{11,13,14}. Because there is little motion between northern Africa and northern South America, it is not obviously necessary to resort to forming these deposits behind dams that cut off the southern Neocomian and Aptian Seas, although the Walvis Ridge and Rio Grande Rise could have acted as such structures (R. Leyden and J. R. Nunes, to be published). Finally, by Albian time (~ 105 to 100 m.y. BP) a wide, shallow marine transgression occurred

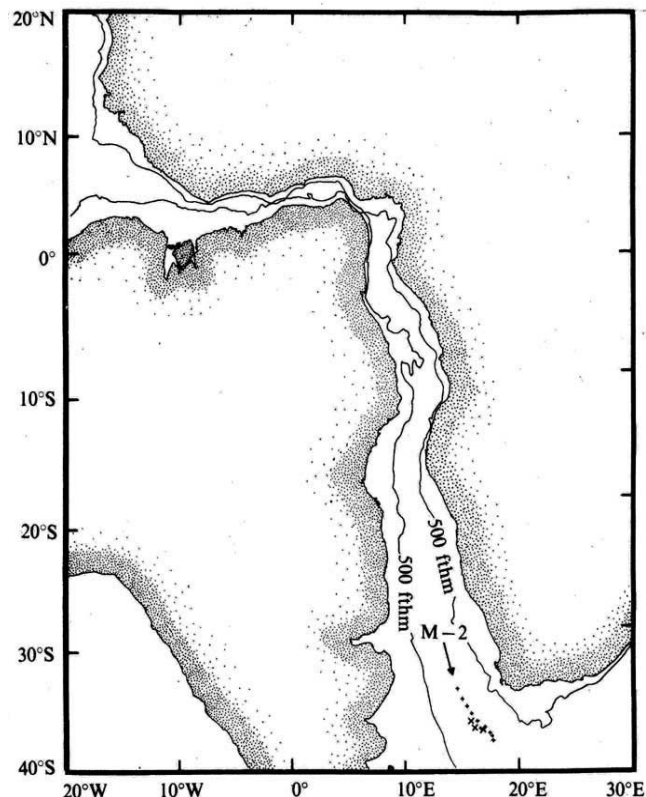


Fig. 3 Palaeogeographical reconstruction of the South Atlantic at 112 m.y. BP (anomaly M-2 time). The reconstruction was made for Africa and the Cape Basin lineations (+) in their present positions by rotating South America and the Argentine Basin lineations (x) first by $+57.0^\circ$ about a pole at 44° N, 30.6° W (ref. 1), and then by -4.6° about a pole at 21.5° N, 14° W (ref. 9). These manipulations bring the M-2 lineation of the Argentine Basin into near coincidence with the M-2 lineation of the Cape Basin.

and the northern South Atlantic was completely open for the first time¹¹.

The oldest magnetic lineations in the Cape Basin are also in close agreement with the ages of the Serra Geral basalts in Brazil that date the initial rifting in that region at 120 to 130 m.y. BP¹⁵ and the Kaoko basalts of south-west Africa whose radiometric age is 114 to 130 m.y. BP¹⁶. The age of the oldest magnetic lineations (~ 127 m.y. BP, anomaly M-12) is also coincident with the marine transgression of southern Africa, southern Chile, and southern Argentina during the Upper Valanginian (~ 127 to 124 m.y. BP)¹². It seems to us that this marine transgression is the direct result of the pattern of early rifting described above. Hallam¹⁷ and Reymont¹¹ studied the palaeontological associations of Lower Cretaceous formations of South America and Africa and concluded that there is enough similarity of the faunas to demonstrate that only a narrow seaway separated Africa from South America during the Neocomian. The Upper Valanginian marine transgression suggested to Reymont and Tait¹² that this was the time that the land masses began to drift apart. Fossil evidence along the south-east coast of Brazil and the western coast of Africa indicates that by Upper Aptian time an arm of the sea had extended northward at least as far as Sergipe and Gabon. The distribution of nekto planktonic ammonite shells indicates that the North and South Atlantic were finally joined in the Lower Turonian, as land connections between Africa and South America in equatorial regions were severed.

We agree that during the Valanginian only a narrow seaway separated Africa from South America because that is the age of M-12, the anomaly that dates the onset of continental drift. We speculate that the Valanginian was not only the time of the initial opening of the South Atlantic, but also of the more

general breakup of Gondwanaland. As the nearest pole of rotation lies to the north, the spreading rate on the ridge that created the Cape Basin lineations must have increased towards the south. Thus, somewhere south of the Cape Basin this ridge met a triple junction, or was transformed to another spreading centre with a faster rate. It is unlikely that the ridge could have been transformed between Antarctica and South America into the Pacific because the Palaeozoic and Mesozoic formations on these continents form continuous sequences that were not fragmented into the Scotia Arc until at least the end of the Andean Orogeny in the Cainozoic¹⁸.

Thus, the ridge was probably transformed to the east into the newly forming Indian Ocean or between the two stable masses that now form east and west Antarctica. The former suggestion is similar to that made by McKenzie and Sclater¹⁹ for the plate boundaries in this area from 75 to 55 m.y. BP. It is an hypothesis that awaits testing by determining the presence or absence of the Mesozoic lineation pattern at the stable margins of the Indian Ocean.

We thank Manik Talwani and Olav Eldholm for pointing out to us the existence of magnetic lineations in the Cape Basin. This research has been sponsored by the US Office of Naval Research and by a grant from the Oceanography Section of the National Science Foundation to the Lamont-Doherty Geological Observatory.

ROGER L. LARSON
JOHN W. LADD

Lamont-Doherty Geological Observatory
of Columbia University,
Palisades, New York 10964

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World-wide Source of Leaf-derived Freezing Nuclei

INITIATION of precipitation over much of the Earth's surface is believed to be intimately related to the development of ice in supercooled clouds. The source, composition and number of small particles (ice nuclei) initiating freezing events in natural clouds are poorly understood. These particles represent a very small fraction of the total aerosol in the atmosphere. The material most frequently held to

represent the majority of ice nuclei are clays, especially kaolin.

In a summary of earlier research, we reported^{1,2} that decomposed plant leaf litters contain large numbers of freezing nuclei and that these nuclei are perhaps responsible for the nucleating abilities of soil particles. (Freezing nuclei are defined as particles capable of nucleating ice in supercooled water. If no distinction is made between freezing and deposition the nuclei are referred to as ice nuclei.) The leaf-derived nuclei (LDN) were found to initiate freezing of supercooled water drops at temperatures warmer than -5°C and to occur in concentrations of up to 10^{10} nuclei active at -10°C per g of decaying leaf. The conclusion that the nuclei are products of decomposition was reached by following the decay of fresh leaves in the laboratory and observing the gradual evolution of nuclei to the stage comparable to naturally decomposed litters. (Extensive chemical analyses have not yet revealed the structure of the LDN but indicate that the nucleating particles probably constitute less than 0.1% of the total decayed leaf litter mass. Filtration tests suggest that the LDN particles are between 0.1 and $0.05\text{ }\mu\text{m}$ in diameter. Heat in excess of 60°C deactivates the nuclei, supporting the suggestion that they are organic in nature.) Though it has not yet been shown that the mechanisms transferring LDN to the atmosphere are of sufficient intensity to account for atmospheric ice nucleus concentrations, it was felt important to establish the extent to which LDN are available on a global basis.

We collected samples of well decayed litter from fifty different dominant tree or grass species across the northern hemisphere. The sampling locations were spread throughout North America, from the Pacific to the Atlantic, and across Europe and northern Asia from Britain eastward through Siberia to Japan. A second set of samples was collected along a transect from Japan through southeast Asia into western India.

Testing of the little samples for freezing nucleus content was done in a standardised manner by inserting 1 g (dry weight) of leaf material into 100 g of distilled water followed by agitation and a 5-min settling period. The resulting suspension was filtered through a paper filter with a pore size of approximately $50\text{ }\mu\text{m}$. The slightly turbid filtrate was tested on a nucleus spectrometer following the principles and procedures outlined by Vali³.

Numerous samples were found to contain freezing nuclei in numbers comparable with what has been reported earlier². Some other samples were found to contain fewer ice nuclei, by factors of up to 10^5 . The abundance of nuclei in a sample appeared not to be correlated with species but showed a closer similarity to samples from the same geographical location. On closer analysis it became apparent that nucleus content is closely related to the climate prevailing at the sample's origin, almost regardless of the species of plant.

According to Köppen⁴, the Earth is divided into six principal climatic zones depending on seasonal temperature and variation, precipitation pattern, and physiography. Of the six zones, three have extensive vegetation (A, tropical; C, humid mesothermal; D, microthermal) and the remaining three have lesser amounts of vegetation (B, dry; E, polar; H, undifferentiated highlands). The type of vegetation growing in each climatic zone is very distinctive for that zone. Data are presented in Fig. 1 for three climatic zones for which a minimum of twelve nucleus spectra per zone is available. For each climatic zone, the highest, lowest and median spectra are plotted. A clear separation between the three zones is evident.

Samples of the genus *Poa* were collected from each of the climatic zones A, C and D. The nucleus contents of the three samples were found to coincide with the typical spectra for each of the zones. Samples of the genera

Fagus, *Oryza*, *Populus* and others were available from two of the climatic zones. In each case the nucleus content followed the climatic trend. Thus, ice nucleus content can be clearly seen to depend primarily on the climate of a sample's origin; it is also evident that the range of nucleus contents for samples from a given zone is quite restricted.

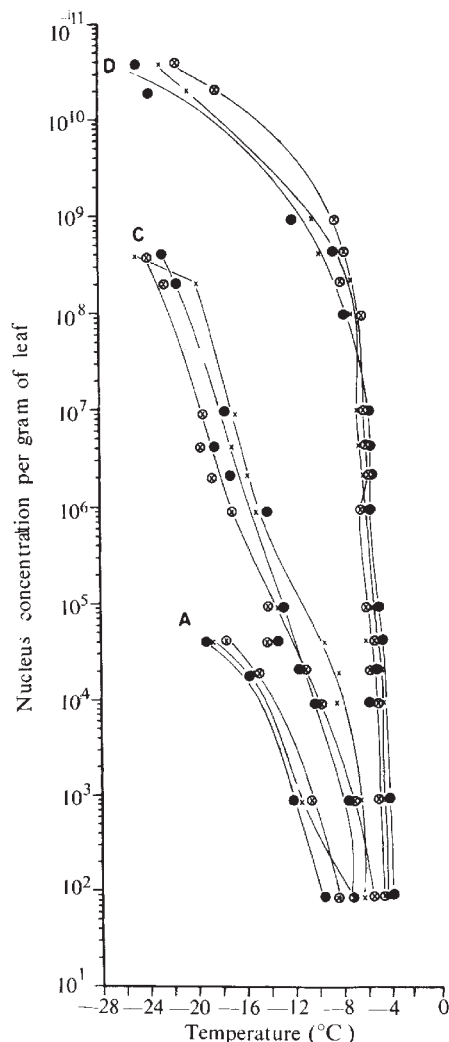


Fig. 1 Freezing nucleus spectra of well decayed leaf litters from A, C and D-type climate zones. For each zone, the highest, lowest and median spectra are plotted.

What factors cause the close tie between nucleus content and climate of growth? Since the process of formation of the freezing nuclei from leaf matter is not yet known, the reasons can only be speculated upon. It is known in general that decomposition is mediated by bacteria and the specific role of bacteria in producing freezing nuclei from leaf matter was demonstrated by Fresh⁵. Differences in microflora among climatic regions might thus be one of the factors. Others of possible importance are the availability of moisture, average air temperature and type of soil substrate.

The climatic dependence of freezing nucleus content in leaf litters does not make itself evident in the concentrations of airborne ice nuclei which have been found to be fairly constant globally⁶. Atmospheric mixing and the possibility that the release of nuclei from litters may also be variable with climate, in an inverse way compared with the availability of nuclei, may account for the observations.

In summary, the world-wide availability of LDN

strengthens the suggestion that LDN may constitute a significant fraction of the atmospheric ice nuclei.

R. C. SCHNELL
G. VALI

Department of Atmospheric Resources,
University of Wyoming, Laramie

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BIOLOGICAL SCIENCES

Rapid Screening Assay for Revertants derived from MSV-transformed Cells

MURINE sarcoma virus (MSV)-transformed 3T3FL cells (S⁺L⁻ cells¹) produced spontaneously and at variable rates flat variants (revertants) from which MSV could no longer be rescued by superinfection with murine leukaemia virus (MuLV)^{2,3}. During the course of investigation of reversion frequency in S⁺L⁻ cells, we have been able to detect revertants by a rapid screening assay technique instead of using the more cumbersome cloning procedure in microtitre wells as previously described^{2,3}. The S⁺L⁻ cell line 3197¹⁻³ was composed of hyper-refractile, loosely attached cells and did not form a compact cell monolayer. Infection of this cell line with MuLV changed the cellular morphology to a slightly more rounded cell type, and increased the tendency of cells to detach readily from the surface of the container. When rescue-negative revertants derived from S⁺L⁻ cells were infected with MuLV there was no observable change in cellular morphology. These characteristics can be used as the basis for a rapid screening assay technique for revertants from S⁺L⁻ cells, the details of which are described here.

The sublines of 3197 cells, 3-321 and 3-360 (ref. 4), grown in modified McCoy's 5a medium with 10% foetal calf serum (Grand Island Biological Co.) were infected with the IC isolate of Moloney leukaemia virus⁵ at MOI > 5 focus inducing units (FIU)⁶, and 1,000–5,000 cells in 5 ml medium were delivered into 25 cm² flasks (Falcon). Flasks were incubated at 37° C for 4 d, then shaken to detach the relatively loose S⁺L⁻ cells; supernatant was removed and flasks were washed twice with medium. Five millilitres of fresh medium were added and flasks were further incubated at 37° C. After a further 3–5 d of incubation, flat, contact-inhibited revertant cell colonies formed and were counted. When S⁺L⁻ cells were infected with MuLV at high MOI (> 5 FIU), MSV was rescued from them about 12 h after infection⁷. At that time, viral interference had developed in rescue-negative revertant cells following MuLV infection, and no transformation of revertants was produced by the rescued MSV. Therefore, revertants remained flat and formed colonies.

The sensitivity of this technique in the detection of revertants was compared with that of cloning techniques^{2,3} in which flat cell colonies were isolated in microtitre wells (Micro Test II tissue culture plate, Falcon) and then tested for rescuable MSV genome by superinfection with MuLV^{1-3,7}. Quantitatively, these two assays gave results which were in close agreement, with the following reversion frequencies: 0.0002 and 0.0003 in 3-321 cultures, and 0.003 and 0.005 in 3-360 cultures, as can be seen in Table 1.

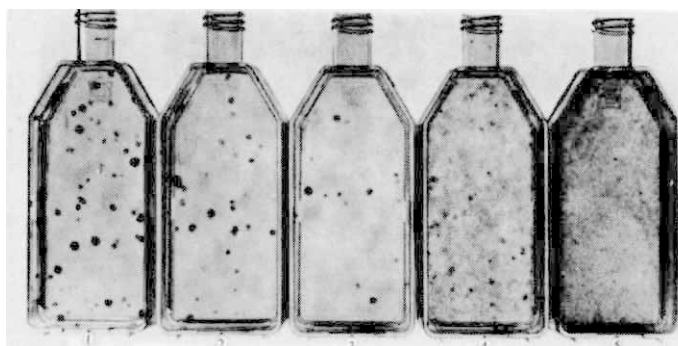


Fig. 1 Reconstruction experiment. Mixtures containing 200 (1), 100 (2), 50 (3), 200 (4) and 0 (5) MSV-revertant cells plus 10,000 S⁺L⁻ cells were seeded into flasks and (1), (2) and (3) were simultaneously infected with MuLV. On day 4, cultures (1-3) were shaken, washed and refed. Photographs were taken after staining on day 9.

The reliability of the rapid screening assay technique for revertants was assured by the following reconstruction experiment. Mixtures containing 400, 200, 100, 50 and 25 revertant 3D-2-14 cells³ plus a constant number (10,000) of 3-321 cells were distributed into flasks, four per group, in the presence or absence of MuLV. At 4 d, cultures were shaken, washed and refed as described above. On day 9, cultures were fixed and stained with Giemsa, and colonies of revertant cells were counted. The average number of revertants in the infected groups was 186, 100, 48.3, 24.5 and 10, respectively. Some stained cultures are shown in Fig. 1. An average cloning efficiency of all groups was 47% which was similar to that of 3D-2-14 cell alone (42%). In uninfected flasks, colonies were small and fewer colonies ($\frac{1}{4}$ - $\frac{1}{2}$ the number in the infected group) were observed. This seemed to result from an interference with the growth of the revertants by an excess of S⁺L⁻ cells. These findings, nonetheless, indicated that the rapid screening assay technique allowed detection of revertant colonies in mixed populations containing a large excess of transformed cells.

This rapid screening assay procedure is not only useful for determination of the spontaneous reversion frequency in S⁺L⁻ cells, but is also valuable for the study of the effects on MSV-transformed cells of physical, chemical and biological agents which enhance the frequency of reversion⁴. Two million 3-321 cells, whose reversion frequency was lower than 0.0003, were exposed to 20 ml of medium containing various concentra-

tions of fluorodeoxyuridine (FUdR) for 1 h at 37° C. At the end of the exposure period, medium containing FUdR was removed, cells were washed twice with medium and dispersed, and 100 cells were plated into 60×15 mm plastic plates (cloning technique), or 1,000 cells were delivered, in the presence of MuLV (MOI>5 FIU), into flasks for rapid screening assay. More than ten plates or flasks were used for each concentration of chemical. On day 8, flasks were examined for the presence of revertant colonies. The results of dose-response in the derivation of revertants from S⁺L⁻ cells are presented in Fig. 2; the optimum dosage of FUdR was 15 $\mu\text{g ml}^{-1}$ which produced a reversion frequency of 0.008, and the same efficiency of revertant detection was found by both techniques. Accordingly, FUdR can be considered as increasing the spontaneous reversion frequency by about thirty-fold. The observed decrease in reversion frequency by high concentrations of FUdR cannot be explained solely on the basis of reduction in cloning efficiency⁴.

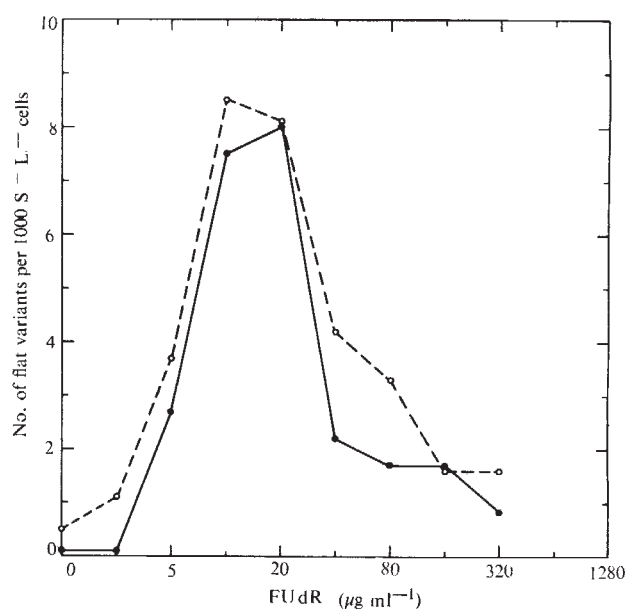


Fig. 2 Dose-response of FUdR in the induction of revertants from S⁺L⁻ cells. S⁺L⁻ cells were treated with various concentrations of FUdR for 1 h at 37° C. At the end of the exposure period, cells were washed and plated at a concentration of 100 cells per plate for cloning technique (●) or 1,000 MuLV-infected cells per flask for rapid screening assay technique (○). On days 7 to 9, frequencies of revertants were determined.

Table 1 Comparison of Sensitivity of Detection of Revertants from S⁺L⁻ Cells by Cloning and Rapid Screening Assay Technique

S ⁺ K ⁻ subline	Assay technique	No. of cells plated	No. of revertants *	Average frequency
3-321	Cloning	1,000	0	0.00018
		800	0	
		500	0	
	Plates†	12,500	3	0.00026
		1,100	0	
		500	0	
3-360	Rapid screening	51,200	11	0.00026
		16,000	4	
		10,000	5	
	Cloning	200	1	0.005
		400	2	
		10,000	33	

* Flat and rescue-negative.

† Plates 0.2 ml of cell suspension containing 1 cell ml⁻¹.

‡ Because of their low reversion frequency, cells were seeded into plastic plates (60×15 mm) at a concentration of 100 cells per plate. On day 9, flat cell colonies were isolated and recloned in microtitre wells.

Preliminary data with Kirsten MSV nonproducer Balb/3T3 cells⁸ similarly demonstrated that the reversion frequencies of a rescue-negative revertant were 0.001 by the cloning technique and 0.0009 by the rapid screening assay procedure. Another subline of S⁺L⁻ cells, FG-10 (refs 1 and 2), revealed reversion frequencies of 0.02 by both procedures.

In summary, the rapid screening assay procedure is a simple and convenient method for the detection and quantitation of MSV-revertants, and is comparable in sensitivity to the cloning technique. It may also prove useful for the investigation of the reversion effects of a variety of agents on transformed cells.

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SHIGEKO NOMURA
KAREN J. DUNN
PETER J. FISCHINGER

*Viral Leukemia and Lymphoma Branch,
National Cancer Institute,
Bethesda, Maryland 20014*

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Prostaglandins as Potentiators of Increased Vascular Permeability in Inflammation

PROSTAGLANDINS are released in inflammatory reactions in animals¹ and in man². The observation that non-steroidal anti-inflammatory agents inhibit prostaglandin synthesis *in vitro*^{3,4} and *in vivo*⁵, and that the comparative potency of these anti-inflammatory compounds is the same *in vitro* and *in vivo* as inhibitors of carrageenin-induced oedema⁶, suggests that prostaglandins may have an important role in inflammation. Prostaglandins (E_1 , E_2 , $F_{1\alpha}$ and $F_{2\alpha}$) evoke increased vascular permeability in the skin of rat and man⁷, which appears to be an indirect effect resulting from mast cell degranulation. The lack of potency of prostaglandins in causing increased vascular permeability on intradermal injection in the guinea pig⁸ has, however, received little attention. We have confirmed this observation (Fig. 1, Table 1) and conclude that in the guinea pig prostaglandins cannot be regarded as chemical mediators which act directly on the vascular endothelium as do histamine, serotonin (5-hydroxytryptamine) and bradykinin. We have therefore investigated a possible alternative role for prostaglandins in inflammatory mechanisms.

The widespread occurrence of prostaglandins in animal tissues together with their mode of action on a wide range of physiological systems has led to the proposition that these substances may have a general function as modulators of cellular responses to a variety of stimuli⁹ (for example, to hormones, neurosecretions, neural transmitters and electrical stimulation). Examples of physiological systems in which prostaglandins may act as modulators include: fatty acid and glycerol production by the epididymal fat pad in response

to adrenocorticotrophic hormone (ACTH) or glucagon¹⁰; altered permeability to water in the toad bladder in response to vasopressin¹¹; gastric secretion in the rat in response to pentagastrin¹²; smooth muscle contraction in response to sympathomimetic amines¹³, and transmitter release from presynaptic nerve terminals following stimulation of the splenic nerve¹⁴. An analogous situation is that of cutaneous pain in man where prostaglandins in conjunction with agonists were shown to induce hyperalgesia and overt pain¹⁵. We have therefore investigated the possibility that prostaglandins may act as modulators of inflammatory reactions. Should prostaglandins modulate altered vascular permeability, two possible sites of action are the microvascular bed itself, or adjacent cells which release inflammatory mediators.

Table 1 Effect of Intradermal Injection of Prostaglandin on Inflammatory Lesions Induced by Histamine and Bradykinin

Dose of material (μ g)	Response $\pm$ s.d. (count in lesion/count in 1 μ l blood)	Difference (count in lesion/count in 1 μ l blood)	Significance (P) (paired t-test)
Histamine (0.5)	104.4 $\pm$ 28.9	—	
Histamine (0.5) + PGE ₁ (1.0)	191.4 $\pm$ 11.6	87.0	< 0.001
Bradykinin (0.5)	144.2 $\pm$ 42.6	—	
Bradykinin (0.5) + PGE ₁ (1.0)	266.7 $\pm$ 40.8	122.5	< 0.001
PGE ₁ (1.0)	32.9 $\pm$ 4.3	—	
Histamine (0.5)	91.1 $\pm$ 3.4	—	
Histamine (0.5) + PGE ₂ (1.0)	123.3 $\pm$ 20.3	32.2	0.05–0.02
Bradykinin (0.5)	102.9 $\pm$ 22.9	—	
Bradykinin (0.5) + PGE ₂ (1.0)	177.8 $\pm$ 20.1	74.9	0.02–0.01
PGE ₂ (1.0)	25.4 $\pm$ 4.5	—	
Histamine (0.5)	88.1 $\pm$ 3.8	—	
Histamine (0.5) + PGA ₁ (1.0)	102.5 $\pm$ 15.3	14.4	0.2–0.1
Bradykinin (0.5)	84.1 $\pm$ 10.4	—	
Bradykinin (0.5) + PGA ₁ (1.0)	125.9 $\pm$ 9.0	41.8	0.01–0.002
PGA ₁ (1.0)	18.6 $\pm$ 1.9	—	
Histamine (0.5)	80.5 $\pm$ 16.6	—	
Histamine (0.5) + PGF _{2\alpha} (1.0)	68.4 $\pm$ 10.5	–12.1	0.5–0.2
Bradykinin (0.5)	88.4 $\pm$ 9.6	—	
Bradykinin (0.5) + PGF _{2\alpha} (1.0)	118.0 $\pm$ 35.5	29.6	0.01–0.002
PGF _{2\alpha} (1.0)	21.6 $\pm$ 3.8	—	
Saline	22.9 $\pm$ 6.4	—	
Uninjected skin	12.4 $\pm$ 1.0	—	

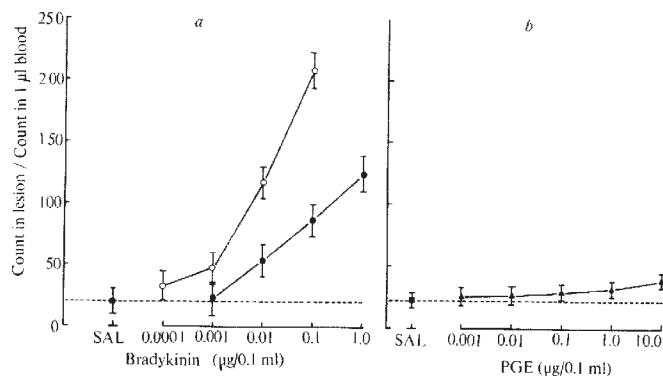


Fig. 1 Dose-response curves in guinea pig skin. Responses represent mean ¹²⁵I-albumin count in lesion/count in 1 μ l blood ($\pm$ 95% confidence limits). a, Bradykinin (●); bradykinin mixed with a constant dose (1 μ g per 0.1 ml) of PGE₁ (○). b, PGE₁ (▲); intradermal saline (0.1 ml) (■).

To ascertain whether prostaglandins act on the vascular bed, their effect on inflammatory lesions induced by intradermal injection of bradykinin and histamine was examined. Inflammatory lesions were evaluated by use of ¹²⁵I-guinea pig serum albumin. Guinea pigs received an intravenous injection of ¹²⁵I-albumin, followed immediately by intradermal injections (0.1 ml) of inflammatory agents using the dorso-lateral skin; doses were allocated to sites according to Latin squares to avoid bias resulting from site and animal variation. After a predetermined time animals were killed and skinned, and disks of skin which included the whole of the lesion were excised with a punch (16 mm diameter) for counting in a well-type γ spectrometer¹⁶. The ¹²⁵I-albumin in 1 μ l of blood was also determined for each animal, to provide a reference.

Figure 1a shows the dose-response relationship between extravasated plasma albumin and the dose of intradermal bradykinin over a 30 min period. When PGE₁ (1 μ g per dose) was mixed with bradykinin before injection, there was a marked shift of the dose-response curve to the left. The increase in slope of the shifted curve prohibits a potency ratio estimate, but at the level of response to 1 μ g

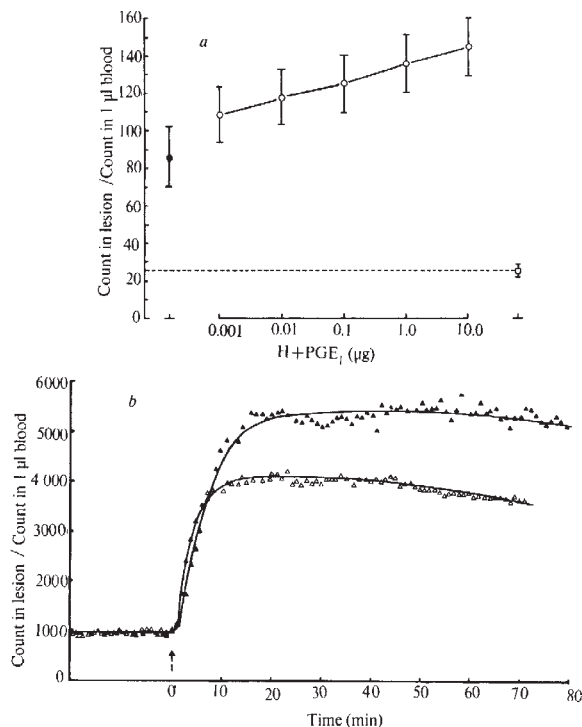


Fig. 2 *a*, H (●), response to intradermal histamine (0.5 μ g per 0.1 ml). H+PGE₁ (○), response to histamine (0.5 μ g histamine per 0.1 ml) mixed with PGE₁ (doses as shown). □, Uninjected skin. Responses represent mean ¹²⁵I-albumin count in lesion/count in 1 μ l blood ($\pm$ 95% confidence limit). *b*, Δ , Time course of inflammatory response produced by intradermal histamine (2.5 μ g histamine per 0.1 ml) at arrow. $\blacktriangle$, Time course of the response to a mixture of histamine (2.5 μ g) and PGE₁ (1.0 μ g) per 0.1 ml.

of bradykinin the presence of PGE₁ at 1 μ g per dose produced a nearly 100-fold increase in the potency of bradykinin. The dose-response relationship of intradermal PGE₁ alone (Fig. 1*b*) shows that the potentiation phenomenon is not simply caused by summation.

Potentiation was also observed when PGE₁ was mixed with histamine before intradermal injection. Potentiation increased with increasing doses of prostaglandin (Fig. 2*a*) and activity was apparent when PGE₁ was present at doses in the order of a few nanograms, indicating a functional significance for the phenomenon.

By a continuous recording technique involving the use of an external γ detector over a single lesion¹⁷, it was shown that potentiation was not accompanied by a substantial prolongation of the response (Fig. 2*b*).

Response potentiation was also observed in varying degrees when histamine or bradykinin was mixed with other prostaglandins (Table 1). In general, potentiation was greater with mixtures of bradykinin and prostaglandin than with mixtures of histamine and prostaglandin (with approximately equipotent doses of agonist). Response potentiation activity ranked PGE₁>PGE₂>PGA₁>PGF_{2 α} . The addition of PGF_{2 α} to histamine produced a reduction in response but this was not significant by the paired *t*-test, $0.5 < P < 0.2$.

We wished to know whether a similar phenomenon might be observed in endogenous inflammatory reactions, where the nature of inflammatory mediators is uncertain and where prostaglandins might act either on the vascular bed itself or on adjacent cells, or at both levels. The effect of local injection of prostaglandins upon three defined allergic inflammatory reactions was therefore examined. Figure 3 shows potentiation by PGE₁ (1 ng–10 μ g) of reactions of Type I (passive cutaneous anaphylaxis), Type III (reversed passive Arthus) and Type IV (delayed hypersensitivity) reactions. For Type I reactions, animals received intradermal injections

of skin-fixing antibody 4 h before intravenous injection of antigen, bovine γ -globulin (BGG) and ¹²⁵I-albumin, PGE₁ was injected into skin sites immediately before the intravenous injection and isotope accumulation in the lesion was determined over a 30 min period. For Type III reactions, animals received intradermal injections of antiserum followed 20 min later by an intravenous injection of antigen (BGG) and ¹²⁵I-albumin. PGE₁ was injected into sites immediately before the intravenous injection and isotope accumulation in the lesions determined over a 2 h period. For Type IV reactions, animals were given intradermal purified protein derivative of tuberculin (PPD) 5 weeks after Bacillus Calmette-Guérin (BCG) vaccination. Sixteen hours later animals received intradermal injection of PGE₁ into skin sites, followed immediately by intravenous injection of ¹²⁵I-albumin, isotope accumulation in the lesions being determined over a period of 2 h. Choice of pulse times in these experiments was based upon previous delineation of the time course of these reactions¹⁷.

Prostaglandins E₁, E₂, F_{2 α} and A₁ are much less active than histamine or bradykinin at increasing vascular permeability (for example, 10 μ g PGE₁ was 1,000–10,000 times less potent than bradykinin). Prostaglandins can, however, cause marked potentiation when injected with histamine and bradykinin, and they are also able to potentiate endogenous inflammatory reactions. In all these situations, potentiating activity could be observed with low concentrations (of the order of a few nanograms) of PGE₁.

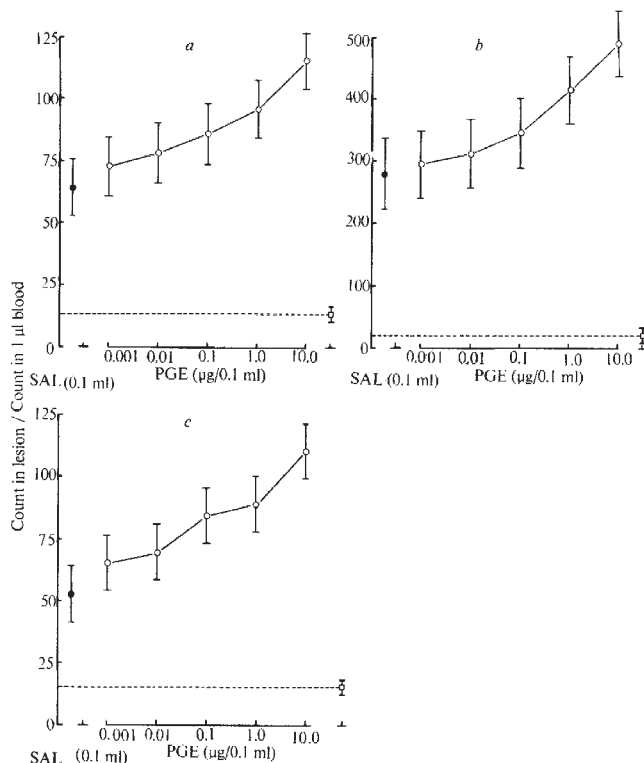


Fig. 3 Effect of a range of doses of PGE₁ on: *a*, Type I reaction (passive cutaneous anaphylaxis); *b*, Type III reaction (reversed passive Arthus); *c*, Type IV reaction (delayed hypersensitivity). ○, Lesions injected with PGE₁ at the doses shown; ●, lesions injected with saline; □, uninjected normal skin. Responses represent mean ¹²⁵I-albumin count in lesion/count in 1 μ l blood ($\pm$ 95% confidence limits).

The mechanism of the potentiation of inflammatory exudation induced by prostaglandins remains unestablished. The possibility that their action may depend on local vasodilatation raising the transmural hydrostatic pressure gradient has not been excluded. Parallels with other physiological systems suggest, however, that potentiation may be due either to sensitisation of agonist receptors on vascular endothelial cells,

or to modulation of cyclic AMP levels in endothelial cells through adenylyl cyclase. Similar mechanisms may control the release of mediators from cells adjacent to the vascular endothelium in the case of endogenous inflammatory reactions, involving mediators from mast cells (Type I reactions), polymorphonuclear leukocytes (Type III reactions), or lymphocytes and macrophages (Type IV reactions). In other species (rat and man) prostaglandins have been reported to increase vascular permeability by release of vasoactive amines from mast cells⁷. Clearly, potentiation activity would amplify inflammatory responses produced by release of vasoactive amines, so that the concept of prostaglandins merely acting as intermediates or 'trigger substances' in these species may represent an over-simplification.

We conclude that prostaglandins, by virtue of their activity as modulators of inflammatory responses, may have a major role in inflammatory mechanisms.

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T. J. WILLIAMS
J. MORLEY

Laboratory of Applied Physiology,
Division of Immunology,
The Kennedy Institute of Rheumatology,
Bute Gardens,
Hammersmith,
London W6

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Prostaglandins, Aspirin-like Drugs and the Oedema of Inflammation

Our discovery that aspirin-like drugs inhibit the biosynthesis of prostaglandins¹⁻³ led to the proposal that this was their main mechanism of action^{1,4}. Several observations have added force to the theory. These include the correlation between relative potencies as prostaglandin synthetase inhibitors *in vitro* and anti-inflammatory activity *in vivo*⁵⁻⁷, the generality of the inhibition in many species and preparations⁸, and the demonstration of release of prostaglandins in inflammation^{9,10} and fever^{11,12}. In addition, prostaglandins of the E series cause an inflammatory response in the skin of rats and man^{13,14} and a fever in cats^{15,16} and man¹⁷.

Prostaglandins cause increased vascular permeability in many species and their potency (on a weight basis) is equal

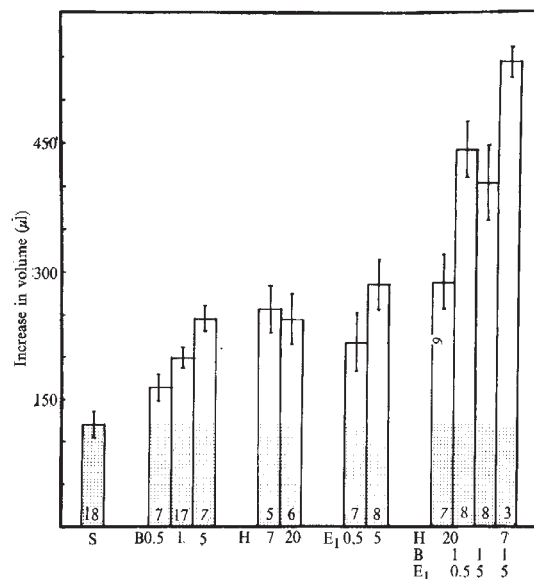


Fig. 1 Potentiation by PGE₁ of the rat paw swelling induced by bradykinin or histamine. The bars show the mean ($\pm$ s.e.m.) increase in paw volume (μ l) 30 min after injection of 0.1 ml saline (S), bradykinin (B), histamine (H), PGE₁ or mixtures as specified. The effects of saline alone are shaded across the figure to allow easier comparison of the added effects of the other substances. Numbers inside the bars refer to numbers of paws used. Note that addition of PGE₁ either to histamine or to bradykinin substantially increased the paw swelling, but addition of bradykinin to histamine did not.

to that of bradykinin and somewhat higher than that of 5-hydroxytryptamine (serotonin) and histamine¹⁸. The oedema induced by prostaglandins is not, however, dose-dependent as it is with bradykinin; indeed higher doses of prostaglandin E₁ (PGE₁) inhibit the oedema caused by other mediators¹⁹. Additive effects, rather than synergism, were also demonstrated between prostaglandins and histamine, bradykinin or carrageenin injections¹⁹.

We have shown that PGE₁ and PGE₂ sensitise the pain receptors to mechanical and chemical stimulation and suggested that the analgesic action of aspirin-like drugs could be explained by the abolition of the sensitisation caused by the local release of prostaglandins during an inflammatory reaction²⁰⁻²². The present experiments were designed to test whether a similar mechanism could account for the pro-inflammatory actions of prostaglandins. We have reinvestigated the interaction between prostaglandins and other putative mediators and carrageenin-induced oedema. Wistar rats of either sex weighing 150-250 g were used. In the first series of experiments, injections (0.1 ml) of different substances were given into the plantar region of the hind paws. Substances used included PGE₁ (0.5-5 μ g), bradykinin (1-5 μ g) and histamine (7-20 μ g); they were given either alone or in mixtures as specified later.

In the second series of experiments, carrageenin (2% w/v in saline) was injected into the hind paws to induce inflammation. All but the control animals were treated with indomethacin (20 mg kg⁻¹, 30 min beforehand in Tris buffer at pH 8). In the indomethacin-treated group, some rats received a mixture of carrageenin and either PGE₁ (0.1-0.5 μ g), PGE₂ (0.1-0.5 μ g), PGF_{2 α} (0.5 μ g), bradykinin (1 μ g) or histamine (20 μ g).

Injections were made into both hind paws in random order; the oedema was measured by the mercury displacement method²³.

Figure 1 summarises the results obtained by injecting inflammatory mediators into the rat paws. To facilitate comparison of the effects of the mediators, above the increased paw volume caused by saline alone, the saline effect has been shaded on the figure. There was a dose-dependent effect of

bradykinin but no significant increment ($P > 0.5$) to varying concentrations of histamine or PGE_1 . These results agree with those of Glenn¹⁹.

The histamine-bradykinin mixture produced an effect no greater than that of histamine alone. The effects caused by mixtures containing PGE_1 were, however, substantially greater for histamine and for bradykinin than those expected by simple addition. Increasing the dose of PGE_1 from 0.5 to 5 μg did not increase the potentiating activity.

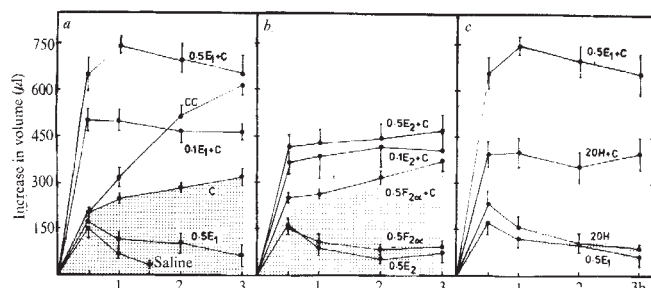


Fig. 2 Potentiation by PGE_1 or PGE_2 of the rat paw swelling induced by carrageenin in the presence of indomethacin. Panel *a* shows the effects of carrageenin alone (CC) over a 3 h period. To facilitate comparison, the swelling induced by carrageenin in the presence of indomethacin (C) is shown as a shaded area in each panel. Prostaglandin E_1 (0.1 μg ; 0.1 $\text{E}_1 + \text{C}$) substantially increased the paw swelling induced by carrageenin, and 0.5 μg (0.5 $\text{E}_1 + \text{C}$) was even more effective. Panel *b* shows similar but smaller effects for PGE_2 but no effect with $\text{PGF}_{2\alpha}$. Panel *c* shows that 20 μg histamine (20 H + C) had a potentiating effect similar to that of 0.1 μg PGE_1 . Curves inside shaded areas in the three panels show the effects of PGE_1 (0.5 μg), PGE_2 (0.5 μg), $\text{PGF}_{2\alpha}$ (0.5 μg), histamine (20 μg), or saline (0.1 ml) given alone.

Figure 2 shows the effects of addition of various substances on the paw swelling induced by carrageenin. Panel *a* shows that indomethacin reduced the paw swelling induced by carrageenin alone. In order to test the effects of exogenous prostaglandins on the paw swelling induced by carrageenin, it was necessary to suppress endogenous prostaglandin formation by pretreatment of the rats with indomethacin. In these animals, PGE_1 , PGE_2 or $\text{PGF}_{2\alpha}$ (0.5 μg ; 5, 4 and 4 experiments respectively) caused no greater paw swelling at 30 min than did saline alone (8 experiments), but their effects lasted for a longer time. There was little or no difference between the paw swelling induced by the three prostaglandins at this dosage, but their effects on the oedema produced by carrageenin in the presence of indomethacin (shown as a shaded area on the graphs) varied substantially. Prostaglandin E_1 (0.1 μg , 5 experiments) potentiated the paw swelling at 30 min and at 0.5 μg (6 experiments) the effect was even greater. Prostaglandin E_2 (0.1 μg , 6 experiments; 0.5 μg , 9 experiments) was about one-fifth as potent as PGE_1 and $\text{PGF}_{2\alpha}$ (0.5 μg , 8 experiments) gave no potentiation. At the time (30–60 min) when the PGE_1 and PGE_2 were producing maximal potentiation of the carrageenin paw swelling they had no greater effect than saline when given by themselves. Histamine (20 μg , 8 experiments) gave some augmentation of the paw swelling induced by carrageenin in the presence of indomethacin but the effects were less than, or equal to, the potentiating action of PGE_1 at 0.1 μg , that is, it was at least 200 times weaker than PGE_1 . Bradykinin (1 μg , 5 experiments) had no potentiating effect on the carrageenin paw swelling.

These experiments support our hypothesis that prostaglandins E_1 and E_2 potentiate the oedema-producing capacity of other inflammatory mediators. Assay of mediators in inflammatory exudate produced by carrageenin in the rat showed release of both histamine and bradykinin in the early phase but that of PGE_2 only after two to three hours⁹. Thereafter, the concentrations of PGE_2 and histamine increased

steadily and paralleled the time course of migration of polymorphonucleocytes into the site of injury²⁴. Our results, which show that indomethacin has an inhibitory effect on the carrageenin-induced oedema as early as 1 h after injection, are in agreement with those of other authors²⁵ and suggest that at the time when there is little or no migration of polymorphonucleocytes there is already a release of prostaglandin by the local cells and that this release potentiates the effects of the other mediators. Phagocytosis by polymorphonucleocytes also releases prostaglandins²⁶, so there could be a contribution to the potentiation from this source also. We propose therefore that the role of prostaglandins in the oedema of inflammation is to intensify the effects of the other chemical mediators. In this respect, their activity parallels that which we found for the pain of inflammation^{20–22}. Such an action explains why aspirin-like drugs only reduce but do not abolish the response to an inflammatory stimulus. For example, in this work and previously^{24,25,27}, the rat paw swelling induced by carrageenin was reduced by less than 60% by high doses of anti-inflammatory substances such as indomethacin.

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S. MONCADA
S. H. FERREIRA
J. R. VANE

Department of Pharmacology,
Institute of Basic Medical Sciences,
Royal College of Surgeons of England,
35/43, Lincoln's Inn Fields,
London, WC2A 3PN

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Incorporation of Rhodopsin Proteolipid into Bilayer Membranes

RHODOPSIN constitutes over 80% of the membrane-bound protein in the outer segment of rod photoreceptors^{1,2}. Absorption of light by rhodopsin leads to large changes in the ionic current of the receptor cell³: excitation of a single rhodopsin molecule transiently (~ 1 s) stops about 10^7 Na ions from flowing across the plasma membrane of the outer segment^{4,5}. The mechanism by which the excited rhodopsin molecule achieves such large reduction in ionic flux is not understood, partly because natural rhodopsin-containing membranes amenable to the experimental methods required to investigate the transport properties of rhodopsin have not been successfully prepared. As an alternative to natural membranes, attempts to form model membranes which incorporate the properties of the photoreceptor have been made. Takagi *et al.*⁶ and Fesenko *et al.*⁷ have reported the incorporation of ultrasonicated fragments of rod outer segments into model membranes. In this study we report the successful incorporation of native, purified rhodopsin into bilayer membranes. This should make possible the investigation of the mechanism by which rhodopsin molecules act in the rod photoreceptor.

Two recent advances have permitted us to incorporate rhodopsin into model membranes. One is the report by Hong and Hubbell⁸ on the preparation of detergent-free phospholipid vesicles containing purified rhodopsin. The other is the report by Montal and Mueller⁹ on the formation of lipid bilayers, in the absence of any organic solvent, by the hydrophobic apposition of lipid monolayers. In the method of Montal and Mueller monolayers of lipids dissolved in a readily volatile solvent are spread on an air-water interface in each of two compartments. The compartments are separated by a hydrophobic partition in which there is a small (about 0.25 mm diameter) aperture. After the solvent evaporates, a bilayer is formed by raising the water level in two compartments above the level of the aperture. The hydrocarbon tails of the lipids in the two monolayers oppose each other across the aperture forming the bilayer. To incorporate rhodopsin into these model membranes, therefore, it was first necessary to form lipid monolayers containing native, purified rhodopsin.

To extract rhodopsin, rod outer segments from dark-adapted bovine retinas (Hormel Co.) were isolated by sucrose flotation, and purified in a discontinuous sucrose gradient¹⁰. Phospholipid vesicles containing rhodopsin were prepared following the method of Hong and Hubbell⁸. Dodecyl trimethyl ammonium bromide (DTAB) (Eastman Co.) (100 mM) which had been recrystallised twice was used to extract rhodopsin. Phospholipid recombinants were made with chromatographically pure egg lecithin (General Biochemicals). Recombinants were made with three different molar ratios of lecithin to rhodopsin: 100:1, 50:1, and 25:1 assuming an extinction coefficient for rhodopsin of 40,600 at 498 nm (ref. 11). Unlike Hong and Hubbell we did not delipidate the rhodopsin-DTAB micelles before recombination with the phospholipid, so the total phospholipid to rhodopsin mol ratio must be larger than what we report here. The detergent was removed by exhaustive dialysis (4 d in the dark at 4° C) against 5 mM Tricine (Tris(hydroxymethyl)methyl glycine), pH 7.0. At the end of

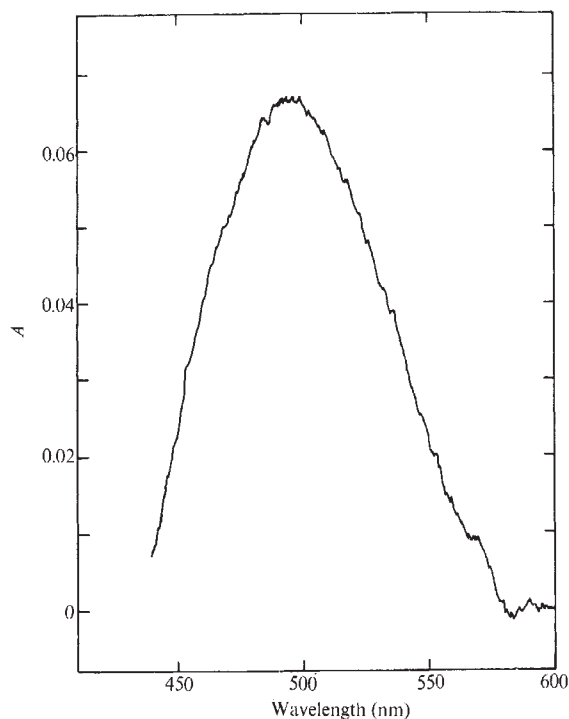


Fig. 1 Difference spectrum of rhodopsin in hexane. The absorption spectrum was measured in a Cary 14 spectrophotometer with the use of a 1 cm path length cuvette in a temperature-regulated jacket (10° C). The spectrum shows a peak with $\lambda_{\max}$ at 498 nm.

the dialysis period the water-soluble rhodopsin lipoprotein vesicles were collected by centrifugation.

To form monolayers, the water-soluble rhodopsin lipoprotein must be extracted into an organic solvent and must not be denatured. In this study we attempted to extract rhodopsin lipoprotein into hexane by charge neutralisation with Ca, since it might be expected that ion-pair formation between Ca and the hydrophilic groups in the lipoprotein would enhance the solubility of the lipoprotein in solvents of low dielectric constant¹². Rhodopsin lipoprotein was dispersed in 4 ml of distilled water in a tube at concentrations of 0.25 and 0.5 mg ml⁻¹. One ml of hexane and 0.2 ml of a 100 mM CaCl₂ solution were added to the dispersion in rapid succession. The tube was vigorously mixed for 5 min and the two immiscible phases were then allowed to separate. Within 30 min more than 90% of the protein was extracted from the aqueous into the non-aqueous phase. Within 6 h the aqueous phase was completely clear indicating total lipid extraction. Extractions were routinely carried out in the dark at 4° C. Control experiments indicated, however, that extraction at room temperature was equally successful. After extraction the hexane phase had a characteristic red colour, was turbid and changed to a distinct yellow colour following illumination.

Absorption spectra in the visible range of the organic solvent phase showed a peak with $\lambda_{\max}$ at 498 nm (Fig. 1) which disappeared upon illumination. This result indicates that we succeeded in extracting native rhodopsin lipoprotein into hexane by ion-pair formation with Ca. We have thus formed a rhodopsin proteolipid, that is, a complex of lipid and protein which shares solubility properties with lipids¹³. Extraction of native rhodopsin was also successful with other organic solvents such as pentane and ether. Attempts to regenerate bleached rhodopsin in the organic solvent by addition of 11-*cis* retinal have failed so far.

In agreement with previously reported data on the extraction of cytochrome c into organic solvents¹⁴, we found that divalent cations (Ca, Mg) were more effective than monovalent cations (Na, K) in extracting rhodopsin into hexane,

and that Ca was more effective than Mg. The turbidity of the organic phase suggests that some water must have been extracted into hexane along with protein and lipid. We have not quantified the extent of water extraction. It is, however, expected that some water could have been extracted since rhodopsin is partially hydrophilic, as suggested by its amino acid composition¹⁵, the presence of carbohydrate residues covalently attached to it^{16,17}, and X-ray scattering data which indicate that rhodopsin in the photoreceptor membrane is partially surrounded by water¹⁸.

The rhodopsin proteolipid in hexane spreads into a monolayer when placed at an air-water interface. These monolayers could be used to form rhodopsin-containing bilayers following the method of Montal and Mueller. Monolayers were spread on a clean aqueous solution surface as condensed films at their own lens pressure. Bilayers were formed upon raising the solution level on both sides of the hydrophobic partition by injecting solution into the two compartments with syringes. We attempted at first to form symmetrical membranes by apposing two monolayers containing rhodopsin proteolipid. The membranes formed under these conditions were, however, extremely unstable. To increase stability we formed asymmetric membranes simply by apposing monolayers of different chemical composition¹⁹. One monolayer was formed with a mixture of glycerol dioleate (Armark Chemicals) and cholesterol (Sigma) dissolved in hexane, while the other was formed with the rhodopsin proteolipid.

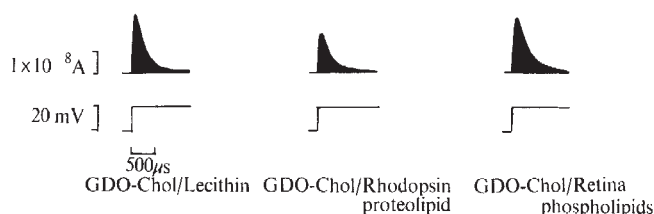


Fig. 2 Membrane current in response to 20 mV voltage pulses across asymmetric bilayers. The upper trace in each record is current and the lower trace is voltage. Voltage pulses were repeatedly applied (5 per s) and the current traces were superposed on a storage oscilloscope. Asymmetric membranes were formed by apposition of two monolayers of different chemical composition. The records presented correspond to three different membranes. In all three membranes one monolayer was formed with a mixture of glycerol dioleate-cholesterol (1:0.26 molar ratio) dissolved in hexane, while the other monolayer was formed with either egg lecithin in hexane, or rhodopsin proteolipid in hexane or phospholipids extracted from bovine retinae (6 mg ml⁻¹) with chloroform: methanol (2:1 v/v) and purified in a silicic acid column. Rhodopsin-containing monolayers were formed with proteolipid extracted for at least 6 h from a 0.25 mg protein ml⁻¹ dispersion in water of either 50:1 or 25:1 lecithin: rhodopsin recombinants. All monolayers were spread over a 5 mM aqueous solution of Tricine, pH 7.0. All membranes were formed across the same aperture (6 × 10⁻⁴ cm²). The membrane capacitance measured by integration of the current records illustrated is: GDO-Chol/lecithin, 1.05 μF cm⁻²; GDO-Chol/rhodopsin proteolipid, 0.67 μF cm⁻²; GDO-Chol/retina phospholipids, 1.0 μF cm⁻².

The electrical properties of the membranes were studied under conditions of voltage clamp. Constant voltage pulses were repeatedly applied across the membrane, and the membrane current in response to these pulses was recorded. Membrane capacitance was determined by integration of the membrane current records according to the formula:

$$C = \frac{\int i dt}{V}$$

where C is membrane capacitance, i is membrane current and V is the magnitude of the applied voltage step. In Fig. 2 we present typical records. Analysis of these and other records is shown in Table 1. Asymmetric lipid bilayers made

with glycerol dioleate-cholesterol on one side and egg lecithin or phospholipids extracted from bovine retinas on the other side are indistinguishable from each other. They both have a capacitance of about 1 μF cm⁻² and a resistance of 10⁶–10⁸ Ω cm². These values are typical of membranes made with a variety of lipids in the absence of any organic solvent. In contrast, membranes made with glycerol dioleate-cholesterol on one side and rhodopsin proteolipid on the other have a distinctly smaller capacitance of only about 0.65 μF cm⁻². In the dark, the resistance of the rhodopsin-containing membrane is comparable to that of the unmodified membrane: 10⁶–10⁸ Ω cm². Thus, incorporation of rhodopsin in the dark does not affect membrane resistance, but does reduce membrane capacitance.

Table 1 Capacitance of Asymmetric Bilayer Membranes

Composition	Capacitance (μF cm ⁻²)	Dielectric thickness (Å) ‡
GDO-Chol*/lecithin	1.0 ± 0.1 (8) †	19
GDO-Chol/retina phospholipids	1.0 ± 0.1 (8)	19
GDO-Chol/rhodopsin proteolipid	0.65 ± 0.08 (8)	29

* Glycerol dioleate: cholesterol (1:0.26 molar ratio).

† Average ± s.d. (number of measurements).

‡ Assuming ε = 2.1 (hexadecane) inside the membrane.

The change in membrane capacitance on incorporation of rhodopsin can arise from changes in dielectric constant, dielectric thickness or both. Careful measurement of the dielectric constant of both the unmodified and the rhodopsin-containing membranes is needed before a complete explanation can be given for the change in membrane capacitance. It is clear, however, that incorporation of a partially hydrophilic protein into a membrane would, if anything, increase the dielectric constant thus increasing the membrane capacitance with respect to that of an unmodified membrane²⁰. Therefore, if we assume that the dielectric constant does not change upon incorporation of rhodopsin, we can calculate a lower boundary for the effective dielectric thickness of the rhodopsin-containing membrane using the expression:

$$l = \epsilon A / 4\pi C$$

where C is membrane capacitance, A is area, ϵ is the dielectric constant and l is the effective dielectric thickness. Estimating 2.1, the dielectric constant of a long chained hydrocarbon, to be the dielectric constant of both the modified and the unmodified membranes, the dielectric thickness of a lipid membrane is 19 Å and the dielectric thickness of the rhodopsin-containing membrane can be no smaller than 29 Å. The hydrocarbon region of the rhodopsin-containing membrane in rods is 28 Å thick^{21,22}. The rapid rotational motion of rhodopsin in the photoreceptor membrane has led Cone²³ to propose that rhodopsin might act as a light-activated diffusional carrier which transports Ca ions by tumbling across the hydrophobic region of the membrane. The fact that the hydrocarbon region of the rhodopsin-containing membrane is thin suggests an alternative mode of action for rhodopsin as a diffusional carrier which does not require the thermodynamically improbable tumbling of a partially hydrophilic glycoprotein into a hydrophobic phase. If excitation of rhodopsin exposes Ca binding sites which are not available in the dark, then the charge neutralisation which might result from ion-pair formation with Ca would allow rhodopsin to sink deeper into the hydrocarbon region of the membrane, much in the way that Ca permits extraction of rhodopsin into hexane as reported here. In the thin hydrocarbon region of the photoreceptor membrane (~28 Å) the large (~45 Å diameter²⁴) rhodopsin molecule need only sink a few Å to cross the low dielectric region. Thus, rhodopsin might translocate Ca ions across the membrane not by

tumbling, but rather by bobbing in the membrane. Indeed, Blasie¹⁸ has interpreted the changes in X-ray scattering by the photoreceptor membrane that follow illumination as resulting from rhodopsin molecules sinking by about 10 Å into the hydrophobic region of the membrane.

The rhodopsin-containing model membranes have so far been short-lived, with an average lifetime of only about 1 min, making the search for light effects difficult. We have, however, investigated the effects of bright flash illumination on the capacitance of these membranes, and have not distinguished any effects within the resolution of our method. Future investigation will pursue the effects of light on the transport properties of rhodopsin in these model membranes.

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MAURICIO MONTAL
JUAN I. KORENBROT*

Department of Biochemistry,
Centro de Investigación y Estudios Avanzados del
Instituto Politécnico Nacional,
México 14, D.F. México

Received August 2, 1973.

* Permanent address: Department of Physiology, University of California, Los Angeles School of Medicine, Los Angeles, California 90024.

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Studies of the intracellular distribution of phages ϕ X174 and T2 in the organs of rabbits and guinea pigs demonstrated that when they were taken up by the cells of the reticuloendothelial system (RES), most plaque-forming units (PFU) became localised in the larger granular fraction (lysosomes and mitochondria) of the cells³. Inchley *et al.* studied the response of mouse macrophages to injected phage T4^{11,15,17}, finding that within 30 min of ¹²⁵I-T4 injection, more than 99% of the phage was phagocytosed by liver Kupffer cells. Inchley also found that T4 PFU could be recovered from the spleen 5 d after the initial injection¹¹. Extensive studies have shown that elimination of colloidal particles is exponential with time regardless of whether these particles were phage^{11,15,17}, animal viruses¹⁸ or inert substances^{1,19}.

Our studies of the fate of phage λ , injected by several routes into NIH germ-free mice, differ from previous studies in several ways. First, previous investigations focused on elimination of foreign particles, either by phagocytosis or by antibody formation, while we were interested in the distribution of phage which survive rapid elimination. Second, most studies have used isotopic label to determine the location of the injected particles without showing whether the particles retained their biological activity, while we assayed for the ability to make plaques. Third, previous investigations concerned tissues known to be involved in the RES, while we were interested in any tissue accumulating phage. Fourth, our phage could be distinguished from possible contaminants by its genetic markers (Table 1). Fifth, the use of germ-free animals precluded interactions with microorganisms in the gastrointestinal tract, although the germ-free mouse system is not an ideally "clean" system for experimental purposes, for leukaemia viruses and other virus-like particles have been found in the thymus glands of such mice²¹⁻²⁴.

Table 1 Pattern of Test Results by which λ pgal₈₅₇CI857 (ref. 20) can be distinguished from Possible Contaminating Phage

Phage	Plaques on pm+ host	Plaques on pm- host	Plaques at 34° C	Plaques at 40° C	Plaques on λ lysogen	Red plaques on MacConkey's gal with gal- host
λ pgal ₈₅₇ CI857	+	—	Turbid	Clear	—	+
Wild type λ	+	+	Turbid	Turbid	—	—
Wild type or virulent phage	+	+	Clear	Clear	+	—

The phage were checked periodically for their ability to transduce the galactose operon, for the presence of CI857 (production of a heat-sensitive repressor) as manifested by clear plaques at 40° C and turbid plaques at 34° C, and for sensitivity to λ immunity as demonstrated by the inability of the phage to plate on a *su*₁₁₁⁺ λ lysogen.

Figure 1 shows that the gross distribution of the virus was tissue-specific, regardless of the injection route. This, however, was not true with force-feeding, which failed to introduce significant amounts of virus to any tissues and spaces examined. Little, if any, virus was detected in the faeces after injection intraperitoneally, intramuscularly, intravenously or *per os*.

By 3 h after infection the blood contained considerably more virus than the peritoneal fluid even if the virus were given intraperitoneally. Within 48 h the virus was cleared from the blood (<10 PFU ml⁻¹) and the peritoneum, no matter where the virus was introduced.

All the organs examined in the infected animals contained viable phage. Of these organs, the spleen had the highest titre. With increasing time, the titre of phage within the liver decreased rapidly. The results were similar with the thymus. Within 3 h after intraperitoneal, intramuscular, and intravenous administration of virus the titre of virus in the spleen in PFU g⁻¹ of wet tissue was higher than any other organ examined. By 48 h

Fate of Bacteriophage Lambda in Non-immune Germ-free Mice

THE clearance of colloidal particles in animals has been studied in several experiments¹⁻¹⁸. The use of bacteriophage in such studies offers a sensitive tool to augment materials such as dyes, radioactive colloids and enzymes for analysing mechanisms of handling foreign particulate material. Furthermore, such use of bacterial viruses may enhance the general understanding of virus-host interactions.

after infection, the blood titre had decreased to zero while the spleen titre still exceeded 10^4 PFU. This difference between the spleen and other organs increased with time.

The titres of phage found in any of the organs and in the two body spaces analysed were higher if the phage were injected intraperitoneally. This might indicate that the phage within the

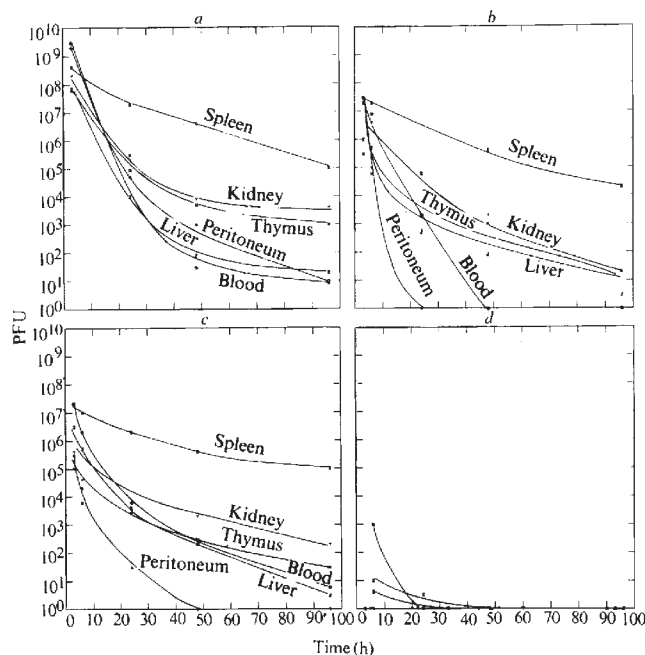


Fig. 1 Plot of the number of PFU g^{-1} wet tissue detected in: blood ($\circ$); peritoneum ($\diamond$); spleen ($\times$); liver ($\square$); thymus ($\otimes$); and kidney (γ); as a function of time after injection of phage by several routes: intraperitoneal (a); intramuscular (b); intravenous (c), and per os (d). *λ pgal₈₅ CI857*, grown vegetatively on *E. coli* C600 (ref. 25), was purified using a CsCl gradient²⁶. NIH albino germ-free mice of mixed sexes were maintained in a plastic Trexler-type isolator unit provided by the Laboratory Aids Branch at NIH²⁷⁻³⁰. Sterility checks were made by streaking samples of organs, faeces, urine and blood onto Tryptone B1 plates to demonstrate the absence of bacteria and by titrating the samples against several strains of *E. coli* to demonstrate the absence of coliphage. All experiments with the germ-free animals were done within the isolator, and not with animals removed from the gnotobiotic environment. All materials passed into the isolator through an air-lock were either autoclaved for 20 min at 121°C, or swabbed with peracetic acid. The acid destroyed the coliphage used in these experiments. 2×10^{12} PFU of *E. coli* phage *λ pgal₈₅ CI857* were injected intramuscularly, intravenously, intraperitoneally or per os. Phage samples in 0.2 ml phosphate-buffered saline (PBS) containing 0.01 M MgSO_4 were injected intravenously into the tail vein or intramuscularly into the quadriceps femoris muscle group. The intraperitoneal injections of phage in 0.5 ml PBS were given in the right middle quadrant caudal to the liver. A mouse restrainer (Fisher) was used to facilitate injection procedures. A polyethylene tube 0.03 inch in diameter, forced down the oesophagus, was used to force-feed the phage sample in 0.2 ml PBS. At 3, 6, 24, 48 and 96 h after injection, mice from each injection group were anaesthetised with ether, the common carotids and jugular veins were cut and the blood was collected in a small test tube. The animals were pinned to a wooden board within the isolator and 3 ml of PBS was injected into the peritoneal cavity. After 1–2 min, the cavity was physically massaged and 0.5–1.5 ml of fluid was withdrawn. Faecal samples were collected when available. The animals were then dissected to remove the spleen, one kidney, the left lobe of the liver and (usually) the left lobe of the thymus. Each of the organs was washed thoroughly with PBS, and final washings were saved and titred to demonstrate that there was little or no phage remaining on the surface of the organs. This indicated that the virus was firmly associated with the organ samples and was not virus from the peritoneal fluid that had coated the organ. All samples were passed out of the isolator for further analysis. A 0.5 ml sample of PBS was added to each organ which was then ground with a sterile sintered glass pestle. Faecal samples were treated in the same way. The samples were titred against DB1 using an agar overlay method³¹. The presence of contaminating viruses was ruled out by tests described in Table 1.

peritoneal cavity were taken up preferentially by the liver and then the spleen, whereas phage injected intramuscularly or intravenously were distributed more uniformly. This agrees with earlier findings³² that compounds administered intraperitoneally are taken up by the portal circulation. Thus the liver maintains the highest concentration of injected substances. Particles injected intramuscularly and subcutaneously were distributed by the heart; because 28% of the cardiac output reaches the liver, the liver should have theoretically fewer particles within its substance when injected by other than the intraperitoneal route. Our results were similar. Therefore the effects, the metabolism and the excretion of phage might be different when injected by varied routes, for varying percentages of injected phage came into contact with the liver.

The spleen retained high titres of injected intact phage (10^6) for prolonged periods of up to 7 d. Inchley also found intact phage in the spleen up to 5 d after infection¹¹.

Retention of phage in the spleen was previously suggested to be due to the fact that "inactivation of antigen occurs much more rapidly within Kupffer cells than within splenic macrophages"¹¹. This interpretation predicted that the spleen, well-endowed with macrophages, would retain lower titres of phage than other tissues deficient in macrophages, such as the kidney. Our data (Fig. 1) suggested an alternative interpretation that the spleen was engaged in non-destructive capture of antigens. The spleen can carry out phagocytosis, but recently a non-phagocytic capturing method utilizing the Schweigger-Seidel capillary sheaths was described³³. This latter mechanism might be responsible for the non-destructive capture of phage that we observed. This ability to non-destructively retain antigen might allow the spleen to serve as a continued source of antigen for the stimulation of antibody formation.

Although it was suggested that non-phagocytic antigen capture by the Schweigger-Seidel reticulum cells required interaction with antibody³³, in our experiments such an interaction was remote, for we were unable to detect neutralising antibody to λ ($K < 10^{-3}$)³¹.

Antigen trapping in the spleen may be closely coupled to antibody formation. An intact spleen is necessary for maximal antibody response¹⁷. The removal of the spleen severely depresses the antibody response in mice, and this defect in antibody formation following splenectomy cannot be corrected by injection of splenic elements¹⁷. Furthermore, in neonatal rats and mice the spleen is an alymphoid organ^{3,4}. The ability to trap antigen appears 2 weeks after birth^{3,4}. Multiple injections of antigen are required during this first 2-week period to stimulate antibody formation, whereas no single injection during this time produces an antibody response⁴. Following the development of the lymphoid elements in the spleen a single injection of antigen stimulates formation of antibodies. These observations indicate that the structural integrity of the spleen might allow cell-to-antigen and cell-to-cell interaction for antibody formation^{2,5,8,13-15,34-39}.

The rapid elimination of phage in intact animals may explain the limited success of phage treatment of infectious diseases⁴⁰ and may interfere with attempts to observe prokaryotic viral gene expression^{41,42} in whole animals. This rapid rate of elimination may be slowed by overwhelming the RES with inert colloidal particles such as Thorotrast (thorium dioxide)^{19,43}.

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MARK R. GEIER
MICHAEL E. TRIGG
CARL R. MERRILL

Laboratory of General and Comparative Biochemistry,
National Institute of Mental Health,
Bethesda, Maryland 20014

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osmotica in the ratio of 1:4 to give the final concentrations of enzymes shown in Table 1, and incubated at 28° C in the dark.

The arrangement of microspores in a few tetrads of *D. metel* (about 5%) was isobilateral but the predominant organisation was tetrahedral. Initially, the four microspores within the massive enveloping wall of the tetrad (Fig. 1a) were naked, but they subsequently developed thin cellulose walls, at which stage they could easily be released from the envelope by gentle pressure. Conventional methods were then used to obtain free protoplasts. The cell walls of both immature and mature pollen grains were resistant to the enzymes used in this study. The mature pollen grains germinated readily and the pollen tubes were then susceptible to enzyme action. Their contents, however, were released as sub-protoplast fragments and not as entities.

Table 1 Effect of Enzyme-Osmotica on Release of Protoplasts from Pollen Tetrads of *Datura metel**

No.	Treatment †	Period of incubation (h)		
		1	4	6
1	CSS	—	++	+++
2	CR	—	+	++
3	CA	— ‡	++	+++
4	H	—	—	—
5	P	—	—	—
6	SDJ	+	+++	+++
7	CSS+H	— ‡	++	+++
8	CR+H	—	+	++
9	CA+H	—	++	+++
10	CSS+P	— ‡	++	+++
11	CR+P	—	+	++
12	CA+P	— ‡	++	++
13	CSS+SDJ	++	+++	++++
14	CR+SDJ	+	++	+++
15	CA+SDJ	++	+++	++++
16	H+P	—	—	—
17	H+SDJ	+	+++	+++
18	P+SDJ	+	+++	+++
19	CSS+H+SDJ	++	+++	++++
20	CR+H+SDJ	+	+++	+++
21	CA+H+SDJ	++	+++	++++
22	CSS+P+SDJ	++	+++	++++
23	CR+P+SDJ	+	++	+++
24	CA+P+SDJ	++	+++	++++

* Percentage yield; —, 0; +, <20; ++, 20–50; +++, 51–80; and +++++, >80. † CSS, Cellulase Onozuka SS (from *Trichoderma viride*), all Japan Biochemicals, 5%; CR, Cellulase Type III (from *Rhizopus* mould), Sigma, 10%; CA, Cellulase Type II (from *Aspergillus niger*), Sigma, 10%; H, Hemicellulase grade II (from *Rhizopus* mould), Sigma, 5%; P, Pectinase, Nutrition Biochemicals, 5% (all concentrations as w/v); and SDJ, snail digestive juice (from *Helix pomatia*), Koch-Light, 2% (v/v). ‡ Occasionally, 1 to 2% of tetrads released their protoplasts.

Nuclear Divisions in Protoplasts isolated from Pollen Tetrads of *Datura metel*

THE significance of haploid protoplast research has been discussed by Bhojwani and Cocking¹. They have succeeded in isolating protoplasts from microspores and bringing about regeneration of cell walls. The occurrence of nuclear divisions in protoplasts isolated from pollen tetrads of *Datura metel* L., a plant in which androgenesis could be experimentally induced^{2,3}, is described here.

Anthers from several buds were pooled in three groups, each of which contained either pollen tetrads, immature microspores or mature pollen grains. Segments of about 5 mm were excised from the central region of anthers and their contents gently squeezed out into 10% sucrose solution. The suspension volume for each group containing an entirely homogeneous cell population was adjusted to about 25×10^4 cells ml⁻¹. Enzymes were prepared as stock solutions in 0.05 M potassium acetate buffer, pH 5.4, containing 10% sucrose. The cell suspensions were mixed with the enzyme-

Protoplasts from pollen tetrads were isolated in twenty-one of twenty-four enzyme-osmotica tested. Mixtures containing a cellulase (irrespective of its origin) or snail digestive juice (helicase) were effective, but pectinase and hemicellulase were ineffective (Table 1). The release of protoplasts in osmotica containing only cellulase (used as controls) was unexpected and contrary to earlier findings¹. This could not have resulted if callose (which is resistant to cellulase) were the only constituent of the tetrad wall. The snail enzyme complex which contains β -1,3- and β -1,4-glucan glucanohydrolases that degrade callose and cellulose, respectively, was comparable in its action with that of cellulase. Cellulase in conjunction with helicase, however, accelerated the rate at which protoplasts were released. The final yield was also higher. Similar observations have been recorded for *Atropa belladonna*, *Lycopersicon esculentum* and *Solanum xanthocarpum* (unpublished data). These findings suggested that the tetrad walls of *D. metel*, and possibly those of the others, contained cellulose in addition to callose. Lysis of either component in the cell wall could bring about a structural

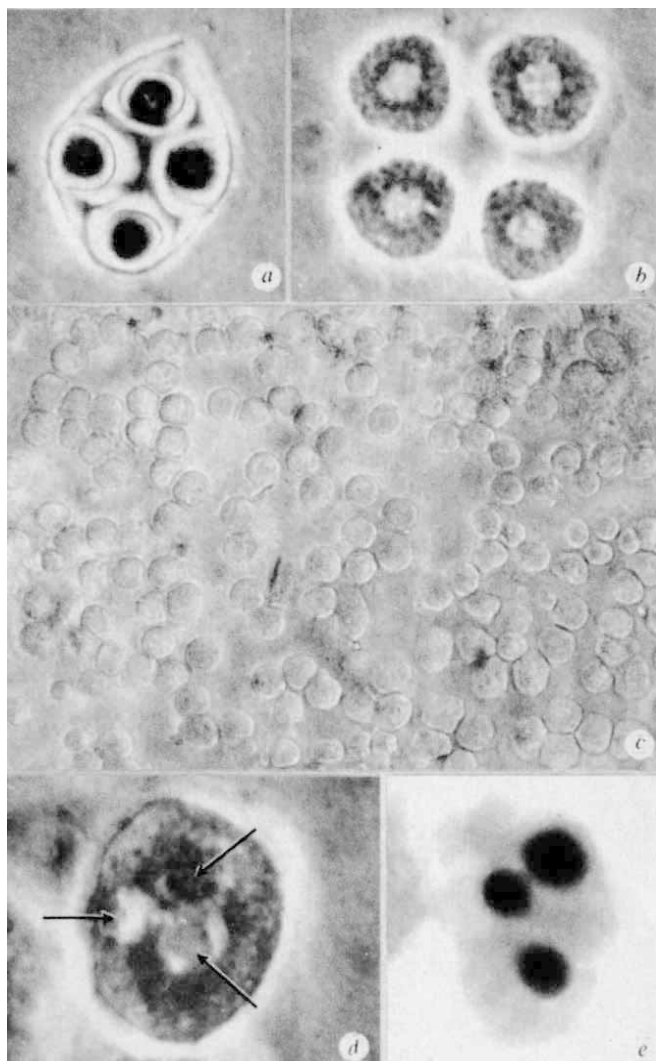


Fig. 1 *a*, Pollen tetrad; observe the massive enveloping wall ($\times 700$). *b*, Group of four protoplasts released from a tetrad; note the dense cytoplasm and large nucleus ($\times 750$). *c*, Pollen protoplasts obtained with cellulase Type II + helicase ($\times 400$). *d*, Protoplast cultured for 5 d showing three nuclei (arrow-marked) without concomitant cell wall formation (phase contrast $\times 1,875$). *e*, A protoplast fixed and stained by carbol-fuchsin method; of the three nuclei one is distinctly larger ($\times 1,875$).

disorganisation and consequent release of protoplasts. The enhanced activity observed with cellulase-helicase mixtures could be due to the complementary and simultaneous action of the enzymes at different sites. That the cell wall composition in the Solanaceae could be species and tissue dependent is further borne out by experiments with somatic cells. Raj and Herr obtained protoplasts from *Lycopersicon*⁴ and *Solanum*⁵ with polygalacturonase, an enzyme that was ineffective in the isolation of protoplasts from *Nicotiana* cells.

The average yield of protoplasts from tobacco tetrads was 35% (ref. 1). In our experiments, the highest percentages obtained were: 29.6 in 1 h, 48.3 in 2 h, 75.4 in 4 h, and 98.4 in 6 h of incubation. The isolated pollen protoplasts were spherical, non-vacuolate and of uniform size, about 10–12 μm in diameter (Fig. 1*c*). They contained dense cytoplasm and a prominent nucleus (Fig. 1*b*). Phenomena such as spontaneous aggregation, sub-protoplast formation and budding that are normally associated with somatic protoplasts⁶ were, however, not observed.

The protoplasts were cultured as hanging drops in a modified White's medium. The nucleus in some of the protoplasts (less than 1%) had undergone two divisions in

5 d of incubation, producing three nuclei unaccompanied by cell wall formation (Fig. 1*d*). One of the nuclei was larger than the other two (Fig. 1*e*), a condition analogous to the male gametophyte *in vivo* which contains a larger vegetative and two smaller sperm nuclei.

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E. W. RAJASEKHAR

Bio-Organic Division,
Bhabha Atomic Research Centre,
Bombay 400 085

Received July 16; revised August 22, 1973.

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The Secretion of Migration Inhibitory Factor by Intact Schistosome Egg Granulomas maintained *in vitro*

TUBERCLE formation and delayed type dermal reactivity are the hallmarks of tuberculosis, yet the relationship between the two has only recently begun to be elucidated. Most experts still believe that the tuberculous granuloma is a tissue response to the irritative effect of mycobacterial lipids^{1,2}. While the strength of this concept made it difficult to establish granulomatous inflammation as a host immunologic response^{3,5} Warren *et al.*⁶ showed that the schistosome egg granuloma is a manifestation of delayed hypersensitivity, as demonstrated by anamnestic reactivity, specificity, and transferability with immune lymphoid cells but not with antiserum. It was subsequently correlated with other parameters of the cell-mediated immune reaction, including delayed dermal reaction, lymphocyte transformation and macrophage-migration inhibition⁷. Similar results have been provided for the experimental tuberculous granuloma^{8–13}. Here we report the secretion of a lymphokine by intact granulomas maintained *in vitro*, further confirming the hypersensitivity character of the schistosome egg granuloma.

Intact granulomas were isolated¹⁴ from the livers of Swiss mice (Carworth, CF1 strain) exposed 8 weeks previously to 200 cercariae of the Puerto Rican strain of *S. mansoni*. Granulomas were washed twice with 150 ml of saline and settled in a conical flask. One hundred granulomas were counted into plastic 35 $\times$ 10 mm Petri dishes, No. 3001 (Falcon Plastics, California) and were suspended in 1.9 ml of RPMI-1640 medium (Grand Island Biological Company, NY) supplemented with 10% heat-inactivated normal human plasma, 100 units ml^{-1} of penicillin, 100 $\mu\text{g ml}^{-1}$ of streptomycin and 2 mmol ml^{-1} of glutamine. Soluble egg antigens (SEA) were obtained from homogenised parasite eggs as described earlier¹⁵. The protein content of this preparation was 470 $\mu\text{g ml}^{-1}$ (ref. 16). For the examination of non-specific reactivity either a mycobacterial culture filtrate (a 10-fold concentrate of *Mycobacterium tuberculosis* strain H₃₇Ra (ref. 17) having a protein content of 5 mg ml^{-1}) or commercial PPD, second strength (Parke-Davis and Co., Detroit, Michigan) was used. Dishes were set up in duplicate or triplicate for each antigen concentration and buffer controls. Supernatants from each concentration of antigen were pooled separately at 24 and 48 h and assayed for

macrophage migration inhibition using the indirect assay of David¹⁸. Peritoneal exudate cells were obtained from 400 g female Hartley strain guinea pigs after 2 d irritation with Klearol, a light mineral oil. The assay was carried out as described earlier⁷. One-half ml volumes of culture fluids were mixed with the same volume of medium and added to duplicate capillaries in the migration chambers. Preliminary testing of the culture supernatants obtained after the first 24 h of incubation gave erratic and mainly negative results. Results obtained from 48-h supernatants are shown in Fig. 1. Assaying the supernatants has the additional advantage of having minimal residues of human plasma and antigen. Percentage of inhibition was calculated as follows:

% Inhibition =

$$100 - \frac{\text{Average migration of normal cells in supernatants of antigen-stimulated granulomas}}{\text{Average migration of normal cells in supernatants of unstimulated granulomas}} \times 100$$

Twenty per cent or greater inhibition was considered to be significant.

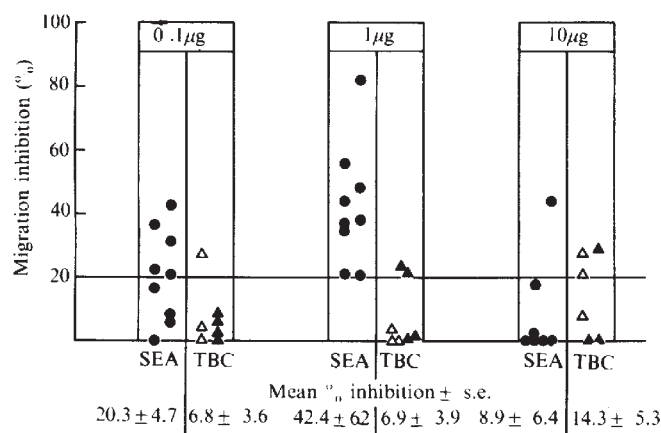


Fig. 1 The inhibition of migration of normal guinea pig peritoneal cells by supernatants from liver granulomas maintained *in vitro*. SEA, Soluble schistosome egg antigens; MCF, mycobacterial culture filtrate; PPD, purified protein derivative.

The isolated granulomas were well circumscribed, compact entities containing one or occasionally more parasite eggs surrounded by fibroblasts, macrophages, occasional epithelioid cells and eosinophils encased in a fibrous matrix. Numerous lymphocytes were visible at the periphery of the lesions, but no plasma cells were seen (Fig. 2). Supernatants obtained from cultures of unstimulated granulomas did not inhibit migration of normal peritoneal cells. SEA up to 40 µg per migration chamber was not inhibitory to the migration of normal peritoneal exudate cells, but both mycobacterial culture filtrates and PPD caused strong (30–50%) inhibition of the migration of cells when added in the concentration of 10 µg per chamber. Thus, the occasional higher inhibitory values of migration seen in PPD or mycobacterial culture filtrate-incubated cultures may be due to the direct inhibitory action of the residual antigens on normal peritoneal exudate cells.

Pooled percentages of migration inhibition showed that incubation of granulomas with 0.1 µg of SEA yielded five of nine supernatants which significantly inhibited the migration of macrophages (mean 20.3 ± 4.7%). Optimal inhibition (nine of nine) was obtained from 1 µg SEA incubated samples (mean 42.4 ± 6.2%) while 10 µg antigen stimulated MIF production in only one of seven samples (mean 8.9 ± 6.4%) (Fig. 1).

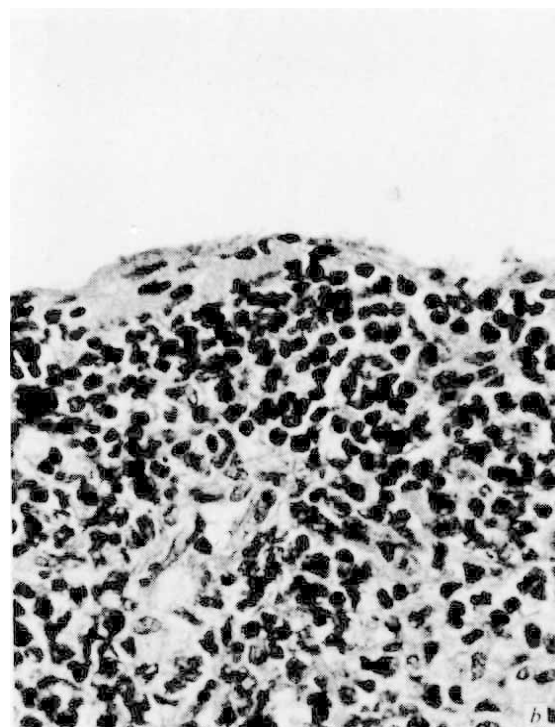
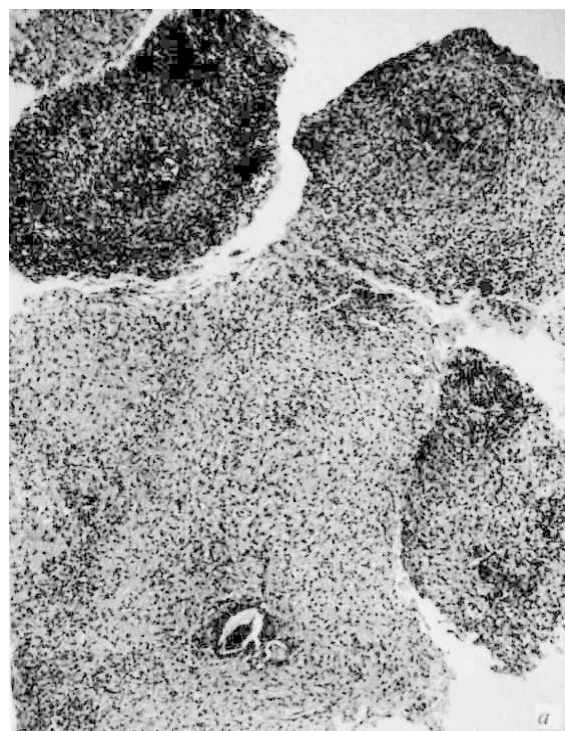


Fig. 2 a, Sections of liver granulomas from mice infected with *Schistosoma mansoni* for 8 weeks. Note schistosome eggs in the centre of several of the lesions. Haematoxylin and eosin × 96. b, High magnification of one of the more highly cellular granulomas, showing predominantly mononuclear cell composition. Haematoxylin and eosin × 384.

Reactions of delayed hypersensitivity are considered to be mediated by a number of soluble substances known as lymphokines^{19,20}. Lymphokines obtained from tissue cultures of antigen-stimulated lymphocytes were shown to elicit inflammatory reactions in normal animals when injected intradermally^{19,21,22}. Recently, extracts of delayed hypersensitivity skin reaction sites were found to possess chemotactic but not MIF activity for macrophages and were shown to produce mononuclear infiltrates in the skin of normal

animals²³. No information is available, however, on the role of lymphokines in inflammatory reactions such as the granuloma.

The granulomatous inflammation around injected schistosome eggs in the lungs of mice is a delayed hypersensitivity immune response⁶. Also, hypersensitivity-type granulomas have been elicited in mycobacterium²⁴, histoplasma- or schistosome-infected animals¹² following the injection of bentonite particles coated with soluble antigens of these organisms, while bare or heterologously-coated particles evoked small foreign body type granulomas. Using this model it was also shown that infected mice, which otherwise reacted with a foreign body granulomatous inflammation around bare particles, developed florid hypersensitivity type granulomas when systemically challenged with the homologous soluble antigen¹². It was surmised that such a reaction could have been caused by the action of circulating lymphokines liberated by the interaction of antigen and the sensitised system. This was shown recently when a large systemic challenge dose of old tuberculin elicited the appearance of MIF and interferon in the circulation of BCG-infected mice²⁵.

While it has been speculated that mediators such as MIF may be instrumental in the formation of the infectious granuloma^{9,26,27} our results provide the first evidence that the granuloma is an immunologic entity capable of secreting soluble mediators on antigenic stimulation. Preliminary observations using concentrated MIF-rich culture fluids coated onto bentonite particles have revealed that MIF can directly elicit a mononuclear granulomatous response.

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DOV L. BOROS
KENNETH S. WARREN
RONALD P. PELLEY

Departments of Community Health and Medicine,
Case Western Reserve University School of Medicine and
University Hospital
Cleveland, Ohio 44106

Received July 5, 1973.

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GENERAL

Ignorance about Limitations to Growth

Forrester¹ and Meadows *et al.*² have presented a family of computer models simulating the future behaviour of some world problems which suggest predicaments of mankind caused by compounded growth. Here I report preliminary results from a different pattern of models which imply that more hopeful outcomes are possible. Both models are assailable oversimplifications.

Proposing a different family of models is not intended as a rejection of the predicament position; indeed, for the present purpose of a broad discussions of assumptions, the predicament models would have to be invented if they did not already exist. The vital policy issues of the next few decades require the clearest illumination of alternatives that critical debate can provide, and in this spirit I regret Gabor's view³: "I hope and I believe that these critics will become silent in time for humanity to avoid the danger of perpetual poverty." I also dissent from Gabor's statement that the computer "can stimulate almost every system if we feed the data into it. It is superior to the human mind only in its ability to deal with complexity." The data have to be selected by the use of assumptions, as discussed below.

The Forrester-Meadows models contain five principal variables (population, food, capital, natural resources and pollution), the state of which is taken to represent the physical aspects of life in this world. This is a serious oversimplification, shared by all fruitful models and theories. Relations are set up between these variables, and the models consist of the growth rates, their multiplication and addition to exert effects on chosen points of the network of connections, and delays between original events and their consequences. Altogether, more than fifty items (computer statements) are used in ref. 1, more than 100 in ref. 2. The number of connections chosen in the process of modelling is larger still, and the assignment of quantities to each relation represents further choices. A description indicating why some connections are not made would require accounts of greater length. ("World III", for example, is chosen from over 7¹⁵⁰ networks formally consistent with the set of items in ref. 2.)

A typical example is shown in Fig. 1. Population increases by those born and decreases by those who died. If enough food is available, birth rate increases and death rate decreases. If, under the pressure of population growth, food production lags behind food requirements, the birth rate decreases and the death rate increases. As people once born die after a delay, (life expectancy), adequate food may "drive" the population to numbers prone to starvation ("overshoot" in control engineering terms), high death rate and severe decrease one to two generations later. This "collapse mode" occurs in all but a few highly "planned" sets of conditions (far from "normal" or "free running" or "intuitively corrected" conditions^{1,2}).

Similar "loops" to that of Fig. 1 connect crowding, pollution and the exhaustion of natural resources to "adjust the population to the maximum that food can support". This statement is, in my view, characteristic of two key assumptions at the base

of the inexhaustible set of the more detailed and technical assumptions in this model family:

(1) "The Malthusian thesis: . . . population is regulated to the food supply" (ref. 1, p. 27) and "the apparent goal of the world system is to produce more people with more (food, material goods, clean air and water) for each person" (ref. 2, p. 86).

(2) No regulatory mechanisms anticipate the Malthusian disaster—hence the predicaments.

Analogous assumptions are made about mounting world use of materials, pollution and crowding to the point of distress. Because both world history, demographic science, economics and the emerging concern for pollution and crowding are rich in varieties of theories, observations, conclusions and opinions, authorities can be found to support almost any assumption.

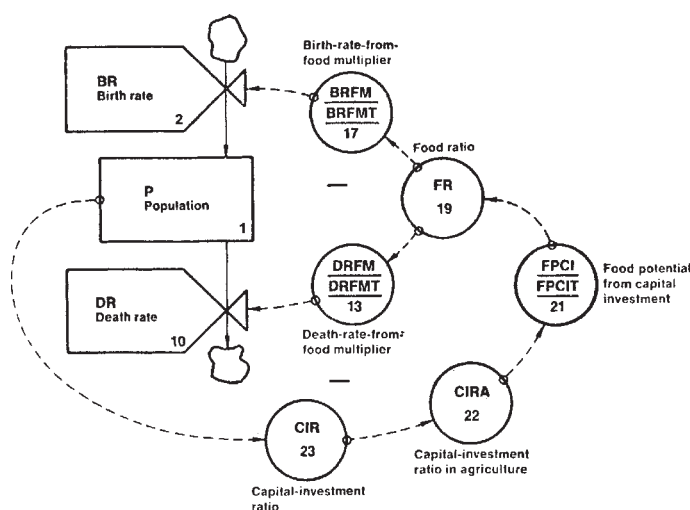


Fig. 1 Negative feedback in population control—after Forrester¹. Malthusian control: "negative loops that adjust population to the maximum that food can support".

No claims were made that refs 1 and 2 forecast world behaviour, or that they have been adequately refined. Yet disturbing implications are drawn from the model behaviour, and offered as cause for world, and decision makers', concerns and future actions.

In addition to the school of neo-Malthusians among demographers prepared to theorise on mechanisms of, and future trends in, population (seemingly a minority of all demographers), there exists another school which emphasises "demographic regulation" and "demographic transition". For the work described here, my chief source has been Bogue⁴; unless a specific reference is given all demographic information has been taken from his work. Errors of selection and interpretation are, of course, my responsibility.

The notion of demographic regulation implies that, in the past (and therefore possibly or probably in the future), adaptation has produced (and, it is hoped, will again produce) conditions of population stability in which a large part (sometimes almost all) of mankind was free from hunger without reacting with rapid population growth. Again, as in the Malthusian thesis, examples abound without being conclusive. (Samoa, the experience of many but not all developed countries to the 30's of this century, etc.) They are reinforced by partial evidence (or conjectures) arising from very early human pre-history, and much evidence from the animal world⁵. Demographic transition implies that such decreases in death rate as are almost world wide are followed, within one to three generations, by corresponding declines in birth rates, bringing population growths back to "manageable" levels—say, to

doubling times of seventy to several hundreds of years. This set of theories has as many critics as the neo-Malthusian theories, and I use it as an undefended assumption. Clearly this pair of notions implies the exact opposite of assumptions 1 and 2 above.

Analogous assumptions are made about natural resources use and pollution: that, early enough, learning of recycling and substitution will forestall disaster in the natural resource sector, and that similar learning rates will rescue us from choking in pollution (pollution is also almost discounted in ref. 2).

Again, I do not defend these assumptions. I merely point out that some of today's key natural resources were not used 100 yr ago, and that many key resources of 100 yr ago have lost this status, such as charcoal, wood as fuel or ship-building material, and horses for transport in developed countries. Such substitution is likely to continue.

The most frightening dangers from pollution arise from uncertainty, as in the DDT chain of effects. With less than 1 part in 1,000 of past production of this pesticide yet active in the biosphere, many sudden bio-ecological disasters have occurred¹⁸. But I refuse to attempt a model of sheer uncertainty for policy guidance.

A further assumption is that of saturation of demand for any specific good per person, accompanied by gradual increase in productivity in developing conditions. This is consistent with refs 7 and 8 and much else since Engel's law of a 100 yr ago. It implies that, at some stage of development, labour is displaced to more and more "advanced" sectors of an economy, according to its taste for each tradeoff, progressively remote from primary needs. This is not unlike references^{1,2} to "global equilibrium", though built into the model at the beginning.

Finally, I assume that the use of this model will be for decision makers concerned to investigate if, from any given starting position (whether now or later) there is at least one feasible path to avoid any condition they define as "disaster". If a broad enough range of feasible paths exists (I believe that, as yet, this seems to be the case) much latitude for choice (in local jurisdictions) still exists, and can be optimised locally. Where possible, I prefer simple local models for ready aggregation to those requiring central decisions.

Having chosen a different school of demography as a source for key assumptions, as I turn to data I face the question how, in this age of science, such diversity of theories can co-exist. Data outside the developed countries before the Second World War are uncertain, and even fairly short term projections were wrong for England and Wales⁹. Population estimates for AD 2000 made in the 1920s have been overtaken and increased to around three to four times the original. Particularly for the large population masses of India and China, the cautions of refs 9 and 10 apply in full, and the comments in ref. 11 are surely optimistic.

Thus demographers have reserved the use of their most refined methods for comparisons between different countries at the same time or over the very short period (1950–1970) for which consistent data can be claimed^{4,5,8,12–14}. Transition models have emerged from some of these studies, but⁴ until the 1980 group of census data is available, no empirical resolution of the transition issue is possible. Even more, firm assignment of causes to population growth patterns seems entirely speculative. I discuss the uses made of these imperfect data on the basis of Fig. 2.

In Fig. 2a, approximate plots are shown for the vital statistics (crude birth and death rates) of France, Japan and Taiwan—the last two with speculative estimates from 1970 to about 2050. Both the fall of death rates (by now essentially world wide) and of birth rates (where it has occurred—and that, compared to biological capacity, has been argued to be almost global) have been more rapid the more recent the observation. Yet this speed-up is more conspicuous for death rates as well as more consistent. Thus there is no statistical evidence of

Malthusian mechanisms at work in the underdeveloped world, though very fast growth is occurring at present.

Birth and death rates in Europe at the time of Rome were each about 42 per 1,000. For stable populations, a lower death rate could lead to much higher growth rates than seem to have occurred before "transitions" (doubling times over 1,000 yr) except for short periods, locally. Higher birth rates were inconsistent with data but also biologically improbable because of the short fertility span of women. Lower birth rates would have led either to rapid extinction or, if reversed by corresponding increases in average food supplies or health, to a regain of the earlier values. Thus the "Malthusian trap" seems to have been homeostatic, except for fluctuations due to plague and drought.

conclusions. The model is less optimistic than either ref. 4 or the UN 1968 "medium" forecast.

The food model has been based on similar mathematical transition curves as Fig. 2c and equation (1), but starting at a low initial asymptote and reaching an upper limit, specified near the best fed European dietary levels in grain equivalent calories; this is almost twice the present world average. For the present, distribution questions within each modelled area are neglected. Increase in food per capita is assumed to arise mainly from intensified agriculture, but in China and India some increase in arable land has been assumed.

I am now in a position to discuss briefly the computer runs partly shown in Fig. 3a-f. I assume that if trade becomes more significant (the reverse seems true at present), it will be to the

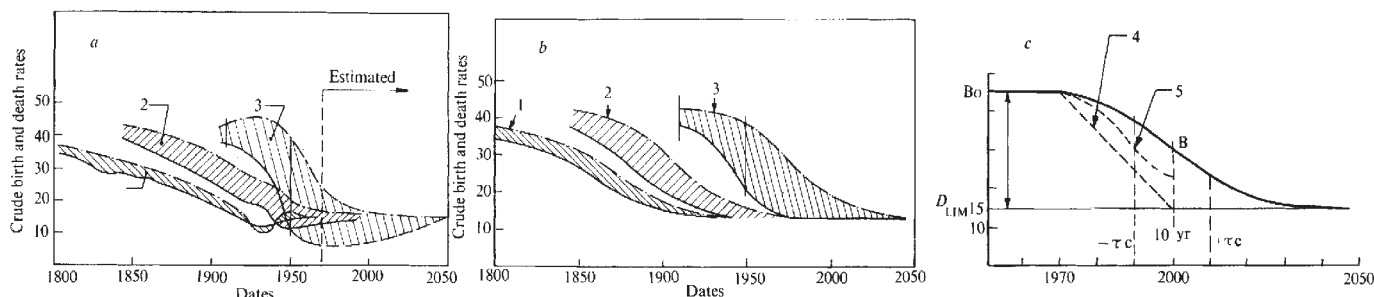


Fig. 2 History of population growth rates in transition: from data to model. —, Deaths; — · —, births; 1, France; 2, Japan; 3, Taiwan. a, Data on growth rates (shaded areas) from France to Taiwan; b, Fermi function for a; c, Fermi function and its parameters for growth rate and constant death rate. 4, Bogue's projection 1970–2000; 5, UN projection 1970–2000; B, sample birth rate model.

In Fig. 2b I show how each of these patterns of vital statistics has been idealised for computation. In spite of the higher rates of change of the crude vital rates, the birth rate fall seems increasingly delayed, from 20 yr average in France, to 35 yr in Japan, to 50 yr in Taiwan. This is chiefly an artefact of selection of the three "prototypes": the inclusion of the European average¹⁴ would have shown 60 to 70 yr, but its overlap with Japan would have obscured the figure. The principal simplification is the omission of the "undershoot" of death rates. The raw data for Taiwan, for example, have death rates of about 6 to 7 per 1,000 since 1963. For a stable population, this requires a life expectancy of 150 yr. For modelling, this transition phenomenon was incorporated in the difference between rates. This implies that the modelled death rates are close to "intrinsic" death rates, but that growth rates are kept "crude". The modelled "birth" rates have no close demographic equivalent.

Each of the curves in Fig. 2b is of the form

$$CBR_{\tau} = (B_0 - 15) (1 - 1/2 \exp [(\tau - \tau_0)/\tau_c]) \quad \text{for } \tau \leq \tau_0 \quad (1)$$

$$CBR_{\tau} = (B_0 - 15) (1/2 \exp [-(\tau - \tau_0)/\tau_c]) \quad \text{for } \tau \geq \tau_0$$

where B_0 is the initial birth rate, τ_0 the date of the inflection, τ_c the time constant.

This is similar in values to the more familiar "logistic" curve, but simpler to compute, and easy to adapt if the particular situation appears to require an unsymmetrical decay, by adding one more to the three parameters required. I show the final model simplification in Fig. 2c where the death rate has been eliminated. Fig. 2c is a direct model of the population growth rate, and its relation to the empirical vital rates is obscured—yet not to the extent of the uncertainty of predicting growth rates into the next century. The assumed constant death rate of 15 would require a world life expectancy of 67 yr over the forecast period. The likely rate of change in life expectancy (80 yr seems optimistic) does not affect my

general benefit if it persists. The pattern of change in population growth was assumed to follow equation (1) with $\tau_c = 10$ yr. This assumes a "transition" to proceed from 90% ($B_0 - 15$) to 10% ($B_0 - 15$) in some 3 generations, between the Japanese and the estimated Taiwan prototypes. The inflection point was estimated crudely from such data as could be gleaned^{4,15} on vital rates for the past 10 to 20 yr¹⁵. Food increases were then adjusted to two constraints: that their slope should match, in per capita terms, the slopes in ref. 11 (p. 4), and that τ_c for food increase should be 15 yr (slower than population change transition) if a feasible fit could be found by simulating changes in τ_0 . This did not prove workable in the case of India, but the demonstrated success of the "green revolution" in terms of yield per acre seemed to justify a use of $\tau_c = 10$ yr for that subcontinent.

Both in terms of future growth prospects and food limitations, India-South Asia is the world's most worrisome area. The first food "peak" is the result of modelling the "green revolution", but not its labour disposal problems. I believe that the amount shown is feasible, but that it would not be chosen. Unemployment or distribution problems are signalled by this feature in the model.

The intent of these very simple models is neither to forecast, even implicitly, the levels reached in either population or food, or to forecast "normatively", to set a target and then to deduce what is needed to achieve it. The question here is much more restricted: given assumptions about population, is it necessary to assume agricultural expansion rates and levels, as well as learning rates that are clearly unachievable? If, on the contrary, such improvements have been obtained in the past, then it is assumed feasible to do so again elsewhere. The pattern of population growth may be capable of greater control than here assumed—then greater latitude exists to deal with food more deliberately and with lower stress on world ecology. My pattern of simulation is only concerned with disclosing "feasible regions" (see refs 6 and 19).

In refs 1 and 2, natural resources played key roles. I assumed above that for gross effects, perceiving and learning early could help us avoid disaster from these major variables. In

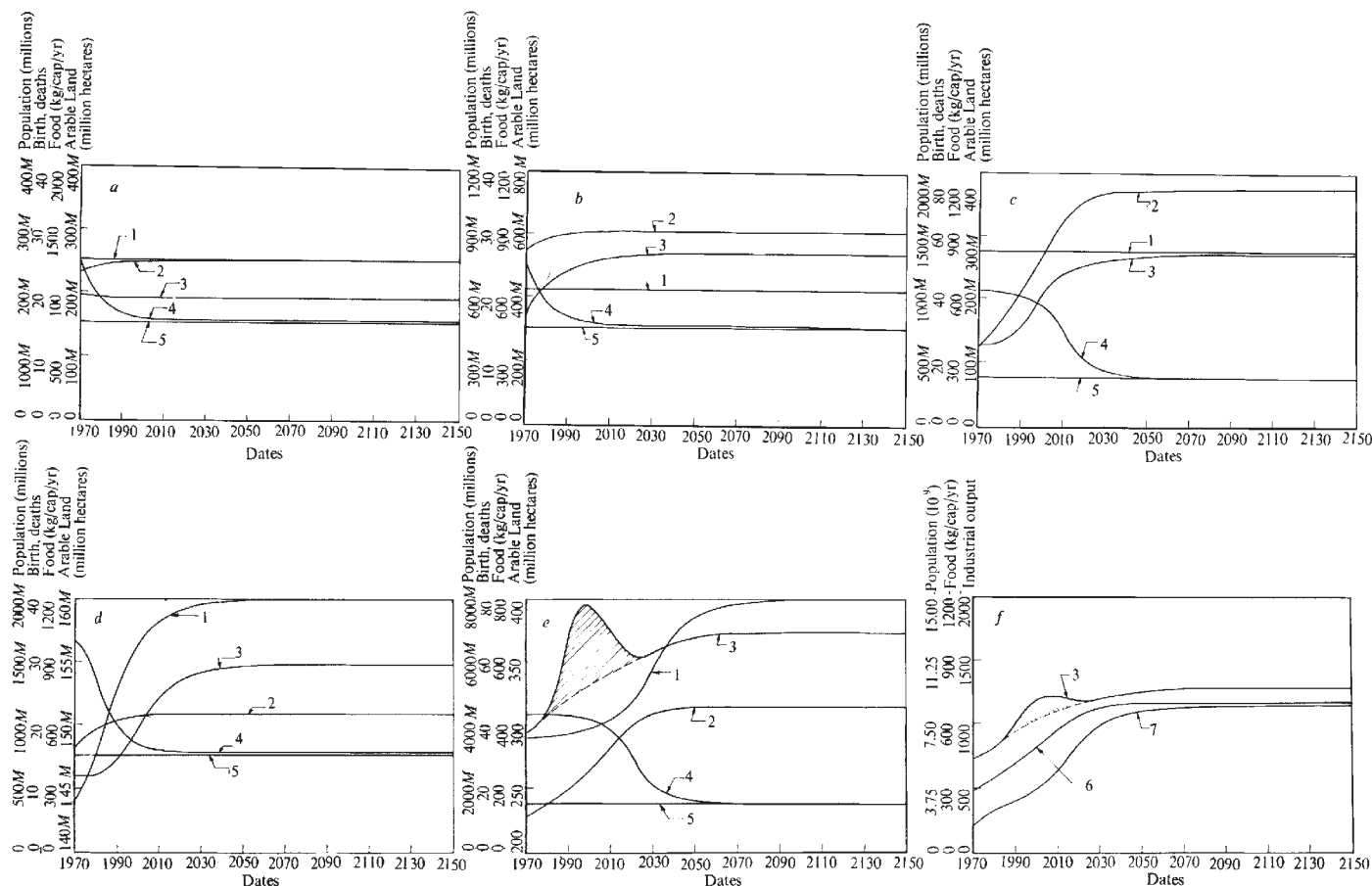


Fig. 3 Feasible food supplies, for modelled populations, in five regions. *a*, North America; *b*, "extended" Europe (including USSR, Japan, Australia and so on); *c*, South America and Africa; *d*, "extended" China (including UN "East Asia"); *e*, "extended" India (including UN "South Asia") and shaded "spurious" area; *f*, summation of *a* to *e* with shaded "spurious" area. This simple addition neglects international trade, at the moment negligible between these groups (except perhaps Europe, the United States and so on, and South America and the developed countries) compared with the uncertainty of data and even more of projections. 1, Arable land (10^6 hectares); 2, population (10^6); 3, food per capita (kg/yr grain equivalent); 4, modelled birth rate per thousand; 5, intrinsic modelled death rate per thousand; 6, population (10^9); 7, industrial output per capita (nominal scaling, \$/yr).

making this assumption, I do not have to presume an exponential or even faster growth of knowledge: for many of these issues, knowledge exists, and as only finite increments of population need be served, the needed increment in knowledge is modest. Its expense may, in fact, lower the future demand in the third world for particular goods now thought desirable in developed countries. Again quite crudely, and assuming multiplier functions opposite in sign to equation (1) for learning but like equation (1) for saturating demand for natural resource intensive industry^{7,8}, I have run the model for each sub-continent and found the increases in "demand" to be "staggered" over several decades (summarised in Fig. 3f). On a similar basis, I have made parameter and policy changes in the model of ref. 2 and have obtained stable and feasible (though different) values (Fig. 4).

Again, no forecasts are implied, but the question is posed: is it inconceivable for us to learn in time? The answer, that it is conceivable, means that more detailed investigations including local preferences and policy choices have a feasible possibility region to explore in medium range studies. These may be urgent: as each decade passes, the progress of events modifies what remains feasible. The principal question is: How may the most rapid solutions be found?

One of the less obvious results of the decrease in death rate (Fig. 2) and its discussion is the disproportionate increase in the average working life span. With life expectancy of 40 yr the working life is 25 yr; but a 24 yr life expectancy corresponds to a working life of only 9 yr. Thus in recent years, the possibility of greatly intensified labour input has not only been a real impulse to improvements in land yields, but has also

become an increasing problem. The number of people is a conservative measure. Thus they provide a better measure of events than money in early stages of development, where exchange has not reached major population groups, or in comparisons across great differences of development¹⁶.

The extensions proposed to the sub-models presently

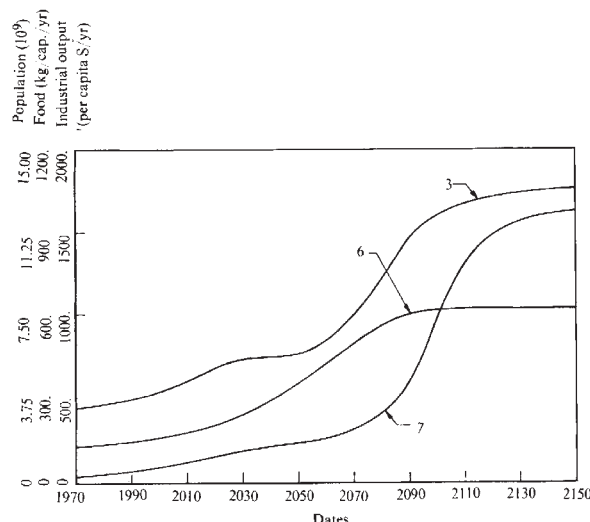


Fig. 4 Meadow's World III, parameters modified to transition assumptions in all relevant "loops". Numbers as Fig. 3.

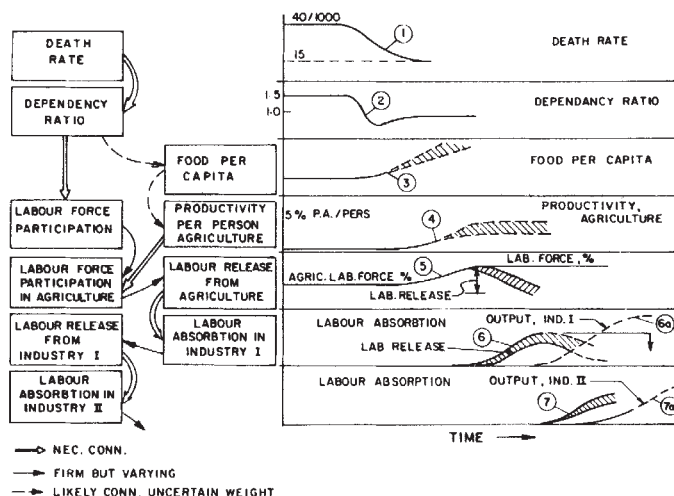


Fig. 5 A "logic model" for the transition from agricultural to industrial development, by labour displacement. As the death rate drops (curve 1) and life expectancy increases, the dependency ratio drops significantly (curve 2) (as extra births and dependants' survival grow more slowly than the proportional working life; (ref. 4, p. 156). The first effect of this is a possible gain in food per capita (curve 3) subject to "policy", which includes patterns of land ownership, income distribution, political organization etc. as well as individual values (at least transitionally). There is room for disaster even if no physical constraint is violated—but there is also a place for examining the emergence of non-physical problems in models of sufficient detail. In curve 4, as some agricultural input labour is accumulating "capital" (this need not require either natural resources or influx of capital funds from abroad, but may be terracing, paddy improvement, much irrigation) the productivity per year per person increases—normally reaching a possible 3–5% per year per person in later, more natural resource-rich stages. Thus (curve 5) the per cent population at work in agriculture will reach a peak, where an increment in "industry I" (depending somewhat on local preferences and endowments) is valued more highly than an increment in food per capita. Curve pairs 6 and 7 show more schematically the entry to "industries I" and "II", which in turn pass from a labour absorbing to a labour releasing pattern, typically (but subject to policies and tastes) involving a time phase where labour is "stored" in the form of capital. In more complex economies, many such changes occur at the same time. Typically, outputs from industries rise after a time delay from the beginning of absorption.

implemented would be an input-output model with formal labour measure and constraints⁶ in which policy can be investigated for the sequential timing of industrial development. As was seen in rice farming in Japan, part of the constraints on sequence are educational: a subsistence farmer will often be unable to move to industries with labour demand for lack of qualification. Policies are thus often needed to adopt labour intensive technologies not efficient in other countries, or to undertake projects because labour of the right qualifications is available, without permitting their wages to fall below subsistence levels.

The logic of such a time sequenced, policy oriented, labour force conserving flow diagram for a closed economy is shown in Fig. 5. It can be extended to trading economies by including more sectors, with appropriate internal costs due to instantaneous wage rates—and equilibria with international prices in each time interval.

Thus at present there seem to be feasible combinations of population increases and food provision within limits of physical and demographic variables. Further problem variables, provided they are saturating in per capita units, can be equally investigated with an expectation of feasibility to physical limits and labour allocation.

Implications of anticipated extensions based on prior work are: (a) As dependency ratios drop, food output per person can increase (as it appears to have done in the past 5 to 15 yr). Further increases can readily come from accumulation of agricultural capital, which may initially be largely labour

intensive given access to knowledge, and cultural and political conditions in which it can be used.

(b) Successive industrial and service sectors can be built up as they become more highly valued than increments in food per capita, or the preceding bundle of industries and services, or traditional income distributions.

(c) Timing and choices are more likely to be determined by taste, the effectiveness of political and economic organisations, and education than by purely physical limitations. Models equivalent to the class outlined conceptually may be used to study many problems whenever such constraints can be quantified.

Some of the teaching of demographers may aid in speeding transition to lower, positive or negative, not necessarily vanishing rates of population growth, and seem worth listing: Provide social security for the old, as soon as is practical, for (ref. 13, p. 718) "with high mortality (among the young), many children must be born to ensure that some will survive to take care of their parents" this dependency must be weakened to help make lower birth rates socially feasible; continue to improve widespread health delivery to lower infant mortality, to aid I; make the rearing of children as expensive as may be consistent with rising income (for instance, by taxing education at the municipal level and emphasis of education for career prospects).

These results and implications are the consequences of the assumptions initially made. My assumptions and results are open to both disagreement and criticism. I have not provided as endogenously controlled a structure as the models proposed in refs 1 and 2. I believe this properly reflects my ignorance of the manifold interactions of physical, demographic, and policy variables.

I believe that future research will show that knowledge of local feasibility will provide more, and more rapid, answers to the world's urgent predicaments than would attempts to implement central technocratic plans.

I thank Mr R. Ritchie for discussions, Mr G. Berry for computational assistance, Professor D. L. Meadows for details of one of his models, the referees for suggestions, and the Waterloo Faculty Research Fund for financial support.

F. ERIC BURKE

Department of Management Sciences,
University of Waterloo,
Waterloo, Ontario

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BOOK REVIEWS

Science and Capitalism

Autocritique de la Science. Edited by Alain Jaubert and Jean-Marc Levy-Leblond. (Collection Science Ouverte.) Pp. 383. (Editions du Seuil: Paris, 1973.) n.p.

It is no longer particularly original or bold to cry out against science and its misapplications. This collection of characteristic texts, mostly of French origin but many translated from English and several from Italian, is significant mainly because it attempts a comprehensive attack from the standpoint of revolutionary socialism. The material is drawn from articles, speeches and pamphlets written by scientists for other scientists on topics ranging from military research to the underemployment of women. With styles ranging from the purest Cartesian analysis to a call for strike action against the *patron* of a *labo*, it is difficult to achieve a unified approach, but the editors have chosen shrewdly and have set each piece in context with a brief introduction. The book can, therefore, be read not only for the individual texts but as a reasonably well balanced exposition of the point of view of a small but not insignificant fraction of the scientific community in France and many other Western nations.

The ideological framework is explicitly Marxist. But there is little evidence of a deep and thoroughgoing analysis of the role of science in contemporary society. An attempt to revise the theory of surplus value to cover scientific work runs away into the sands, and Roqueplo's incisive "eight theses" succeed admirably in not distinguishing between capitalist and socialist science. For most of these authors (including the editors) it seems that a primitive conception of the class struggle and a gut reaction in favour of the correct side in various wars (especially Vietnam) are sufficient ideological justification for political comment and action.

This simplification of the historical and sociological background is a grave defect in the discussion of the militarisation of research. It is easy to renounce financial support from defence organisations and to denounce academic scientists who put themselves at the service of the soldiers in a manifestly unjust war. But the roots of gangsterism, tribalism, patriotism, and nationalism are not nourished exclusively by capitalism: and a brief reference to "state capitalism" does not deal adequately with science in the Soviet Union, for example, which is equally regimented and perverted towards war.

Other noxious applications of science and technology are also interpreted as obvious consequences of the devotion of the capitalist ruling class to the maintenance of their power and profits. But several forceful theoretical papers at the beginning of the book make much of the practical incompetence of technocracy and of scientism. In their political and economic analysis the authors attribute too many of our present follies to clever conspiracies by the power élite, and do not allow sufficiently for the misplaced but universal popular belief that social problems can be solved by specialist skills and technical expertise. This applies particularly to the state of science in the Third World, where much more positive thinking is needed about how to bring genuine scientific benefits to the people. Bad education in and about science can certainly be blamed, but cannot itself be entirely explained away as a reflection of class domination.

Coming nearer home, the discussion of the actual position of the scientific worker is much more realistic. Whether or not this exemplifies the Marxian prediction of the general proletarianisation of the professional classes ("lackeys of the bourgeoisie"?), the increasing exploitation and repression of the individual scientist in the era of bureaucratic big science is a very significant phenomenon, whose psychological and political consequences are vividly depicted in these pages. Some of the current problems emphasised here, such as the gross abuse of power by research bosses, are exacerbated in France by the peculiar organisational structure of universities and scientific institutes, but we must not be complacent about such serious issues as graduate unemployment, the equivocal position of graduate students, uncertainty of tenure amongst research workers, the subordination of skilled technicians, etc. Here again, the plea for solidarity in the face of the class enemy does not resolve all questions. The relationships between an élite of *mandarins* and the body of younger *scientifiques* from whom they have been selected by harsh competition are not exactly equivalent to those between capitalist and worker, and belong more to anthropology than to political economy.

Perhaps I have said enough to show that "self-criticism" of science is an essential activity, by which many matters of the most serious concern can be brought to light. But to point a finger of bitter censure at a scandal, a crime, or an injustice, is only the first step. An adequate analysis and reform—of society

as well as of science—demands an eye for relevant evidence, an open mind towards many theoretical possibilities, and perhaps a little more of the intellectual modesty and scepticism that scientists are themselves supposed to acquire through practising their profession.

JOHN ZIMAN

Irradiating Bone

The Effects of Irradiation on the Skeleton. By Janet M. Vaughan. Pp. xvi + 297. (Clarendon: Oxford; Oxford University: London, March 1973.) £7.75.

THERE is now a large body of information on the important and, at times, emotive subject of the effects of irradiation on bone. This has appeared for the most part in the regular journals but considerable numbers of researches have been published in books reporting the proceedings of specialist conferences. In her book, Dame Janet Vaughan, herself a researcher of great distinction in this field, has brought together these scattered and largely uncoordinated researches into a well informed and balanced synthesis. The book is written from the biologist's viewpoint but has the merit that the biological findings and the physical properties of radiation are related in an unusually perceptive way. The result makes rewarding reading for those in both the biological and physical sciences.

At the beginning of the book the nature of radiobiological action and the characteristics of ionising radiations are dealt with briefly, with consideration of the structure and physiology of the skeleton that are relevant to the irradiation of bone. There follow two chapters discussing in detail the tissues of bone that are at risk, the types of radiation induced cancer that can arise, and the sites of the tissues of tumour origin. A chapter is devoted to the effects of external irradiation, analysing the evidence, for example, of leukaemia induction in human populations, and the problems of internal irradiation are then considered generally in chapter 6.

A most important part of the book deals individually, in separate chapters, with the well known bone-seeking radionuclides: radium, with the dramatic series of radium poisoning cases that occurred mainly in the earlier decades of this century; the strontium isotopes; the isotopes of plutonium, americium and thorium that are deposited on bone surfaces; lastly radiophosphorus and other less known and less used radionuclides. One of the most useful features of the book is a bibliography

of some 700 papers, quoted with full titles, together with the page numbers in the text to which they refer. This is far more useful to a reader than an author index.

The book is written with great lucidity and is well produced with only very few and very minor misprints apparent. The synthesis achieved in this book will be a most valuable asset to those actively working on bone, but it should have a wider appeal in other fields, for example in nuclear medicine, radiotherapy, cancer research and radiation protection. This work will remain an authoritative and enlightening guide to the long term researches that are going on in many laboratories on the effects of skeletal irradiation.

F. W. SPIERS

Animal Sociology

Organisation in Animal Communities: Experimental and Naturalistic Studies of the Social Behaviour of Animals. By Hilary O. Box. Pp. 251. (Butterworth: London, March 1973.) £5 cloth; £2.50 paper.

THIS book, which grew out of a course of lectures given to psychology students at the University of Reading, touches upon a wide range of behavioural phenomena which can loosely be described as social in the sense that in some way they concern interactions between animals. There are descriptions of the social life of many animals and the book is a quite useful, although cursory, account of some of the work which has been done on social behaviour. "Social" is taken very broadly, and mimicry and parasitism are among the subjects undertaken. In addition there are sections on the influence of early experience, particularly deprivation of various sorts, on subsequent social responses, a chapter on communication and a brief survey of the social behaviour of some domesticated animals. The effects of overcrowding and the role of behaviour in the determination of animal numbers are also discussed.

Detailed and comprehensive coverage of all these topics is clearly impossible in only 251 pages, but even with this space limitation, one would have thought that there should have been room to discuss certain important questions which are in fact omitted or not faced squarely. For example, it is surprising that in a chapter which compares insect and human societies, there should be no mention of the fact that the apparent "altruism" shown by many of the social insects is probably related to the uniquely close genetic relationship between individuals in a colony¹. To say that "We now accept that social relationships have facets of both com-

petition and mutual aid" (page 6) without discussing such variables as the degree of genetic relationship within a social group simply sidesteps important questions of how natural selection works.

In short, this book has been written by a psychologist, and it shows.

MARIAN DAWKINS

¹ Hamilton, W. D., *Am. Nat.*, **97**, 354 (1963).

Limited Omnivorousness

Seed to Civilization: The Story of Man's Food. (A Series of Books in Biology.) By C. B. Heiser jun. Pp. xii+243. (W. H. Freeman: San Francisco and Reading, July 1973.) £3.60 cloth; £1.50 paper.

MAN can appropriately be described as omnivorous. Nevertheless, like other animals, his selection of food is influenced by the complex web of compulsions by which his behaviour is moulded. That is to say, he is subject to the natural history of the species. This is as true today as it ever was. As Professor Heiser points out at the beginning of his book, there is no reason to assume that we are any more intelligent now than were the people who invented agriculture ten thousand years ago. It is, therefore, not surprising that even after having described, for the benefit of the general reader for whom this popular exposition is intended, a varied selection of fact and opinion he reaches the conclusion that "the explanations of why and how man 'invented' agriculture . . . are far from certain".

The valuable substance of the book is contained in the chapters in which the origin as human food of the species of animals and plants selected for domestication is described. There is an interesting narrative of what is known of the dog's becoming in 8400 BC man's dumb friend, with a charming illustration of a clay figure from Mexico of a dog specially fattened on maize for the table. The history of the sheep as mutton goes back eleven millennia and the goat about as far. Cattle came later although aurochs, it seems, were worshipped for a long time before they were eaten. The stories of the more exotic animals, the turkey and the Muscovy duck from the Americas, the guinea pig, and the llama from Peru, are narrated as well. It is not surprising that Heiser, a botanist, devotes forty-eight pages to an excellent chapter about grasses, ranging from wheat to bamboo. This chapter, like the rest of the book, is well illustrated with drawings and photographs from many parts of the world and many periods of history. Other chapters deal with legumes, roots, the coconut and odds and ends such as

the Cruciferae, comprising a dozen forms from cabbages to rutabaga, with gourds, nuts, coffee and pepper.

All this is informative, interesting, wide-ranging and well suited for the students of general biology, economic botany, anthropology and home economics at whom, according to the publishers, the book is aimed. A three-page chapter about nutrition is less satisfactory and seems a whit perfunctory. That the only table in it should be of the amino acid contents of various proteins owes more to today's fashion than to the major priorities of physiological need. But it is in his last chapter that we leave behind such delights as the account of the breadfruit, *Artocarpus altilis*, and the troubles that Captain Bligh encountered in transporting 1,000 young breadfruit trees from Tahiti to the West Indies (he succeeded in the end). Instead, there come the all-too-familiar ill-thought-out adumbrations about the population explosion and the "corrupt, inefficient and unstable governments" from which hungry nations suffer. There are quotations from strings of those pessimistic books, mostly written by chemists and biologists, about what "government" should do to succour developing nations. Not everyone agreed with all the rude things that Professor Wilfred Beckerman had to say about the blunders of chemists and biologists when they ignore the existence of political economy as a well established discipline in its own right; but enough of them were sufficiently incontrovertible, one would have thought, to discourage otherwise well-judging authors like Professor Heiser from allowing their feelings to draw them away from the topics upon which they are worth reading to the ritual obeisance to the starving millions.

MAGNUS PYKE

Development

Developmental Biology: Its Cellular and Molecular Foundations. By Maurice Sussman. (Foundation of Modern Biology Series.) Pp. xvi+297. (Prentice-Hall: Englewood Cliffs, NJ, and Hemel Hempstead, March 1973.) £3.50 paper.

DR SUSSMAN'S book is written in an engaging and buttonholing style that has the vigour (and the jokes) that will be familiar to those who have heard him lecture. This inimitable style is admirably suited to his purpose which is to demonstrate "the extraordinary power of science as a method of asking questions properly and answering them with rigour." Much of the book is written in the Socratic tradition as interpreted by modern molecular biologists and provides an excellent and compelling introduction to this approach as well as to

the fundamental aspects of developmental biology. There is a danger, of course, that the beginning student (who is admirably catered for with two introductory review chapters) may not realise that what is being presented is a particular point of view. The preface makes this quite clear but I would have liked to see, perhaps in the bibliography which is given at the end of each chapter, some reference to opposing viewpoints to counter the somewhat dogmatic tone of parts of the text. I doubt, for example, if all would agree that "the only reasonable interpretation" of Dr Mintz's experiments on allophenic mice is the one that she has suggested; and the treatment of morphogenetic fields is curiously old fashioned. These are, however, minor criticisms of a book which can be recommended to both undergraduate and postgraduate students and which will be invaluable as a source book of provocative and pungent statements for those who organise seminars and set examination papers.

J. M. ASHWORTH

Bird Biology

Avian Biology. Edited by Donald S. Farner and James R. King. Taxonomic Editor: Kenneth C. Parkes. Vol. 2. Pp. xxiii+612. (Academic: New York and London, December 1972.) \$32.

SOME ten years ago, A. J. Marshall edited two volumes on the biology and physiology of birds. This volume is the second in a series of three which provide an updated and much needed replacement for Marshall's work. There are new editors, almost all new authors, a different organisation, and more complete coverage.

The volume at hand (volume 2) has three chapters dealing with feathers; the remaining six deal with specific physiological systems such as respiration and circulation. This selection can best be evaluated in the context of the complete series. Volume 1 (already published) has four chapters of more or less classical ornithology and seven oriented towards ecology. Volume 3 (to be published) will deal with reproduction and endocrine systems (four chapters), and with senses and behaviour (another four chapters).

Does this cover the area of avian biology? One could instead ask, what are the most characteristic aspects of bird biology? It seems that these are (1) birds are warm blooded and have feathers, (2) they fly and migrate over long distances, and (3) they have a characteristic mode of reproduction. Some of these subjects are well covered; feathers have three chapters of volume 2, and reproduction will come in volume 3. But there are no individual chapters on bird flight, on migration,

or on thermoregulation. I find a lack of balance here, for endocrinology will have three chapters, and substantial sections on endocrinological control will appear in two more.

Volume 2 contains nine chapters which, as can be expected, are of uneven quality. Most presentations are good and a few are outstanding. Some could be criticised. Chapter 2 ("Patterns of Molting") is from the beginning steeped in terminology which is poorly or not at all defined, and is difficult to follow for a non-specialist. Chapter 7 ("Nutrition") is, as the author states, restricted mainly to the domestic chicken. True enough, most nutritional studies on birds are on chickens, but nevertheless I see no need for the extensive discussions of animal husbandry and the many tables on the nutritional value of commercial feed ingredients. A stronger editorial hand would have been helpful for this chapter, and for the following one ("Intermediary Metabolism"), which seems to be well organised and contains much information but suffers from lack of perspective. With these items to criticise, we are left with a volume that contains mostly good and excellent papers.

There are separate indices for author names, for bird names and for subjects. The publisher deserves praise for making these very helpful tools available to the worker who uses the volumes for constant reference.

KNUT SCHMIDT-NIELSEN

Elementary Particles

Particle Physics: An Introduction. By M. Leon. Pp. xii+268. (Academic: New York and London, March 1973.) \$14.50.

PARTICLE physics is a very difficult subject to teach at introductory level. It has a vast glossary of jargon and there is a large set of intriguing and profound data. But the theoretical framework, which will one day unify the subject, is still lying about as a kit of parts. The kit may be almost complete, but no one has been able to put it together.

This book treats the main theoretical components in an admirably concise way. There are reasonably thorough treatments of scattering theory and quantum-field theory, with brief discussions of quantum electrodynamics, hadron dynamics and weak interactions. Particle properties are presented, with emphasis on symmetries, including SU(3). Such recent developments as dual models, or unified weak and electromagnetic theories, are quite rightly omitted.

Although the preface claims that this text is useful for "seniors and graduate students", the material is too advanced for most undergraduates. This is

probably inevitable in a book which covers so much of the theoretical kit. A sensible starting point for undergraduates is the much more experimental book of I. S. Hughes (Penguin library of physical sciences). For first-year postgraduates, however, this book promises to be extremely useful.

DAVID J. MILLER

Neonatal Anatomy

Functional Anatomy of the Newborn. By Edmund S. Crelin. Pp. xii+87. (Yale University: New Haven and London, February 1973.) £3.50 cloth; £1.75 paper.

THIS somewhat dry and colourless book is an attempt by an anatomist to provide "a concise guide to be used by all personnel involved in one form or another with the newborn infant, including students". The author is a consultant to the Newborn Special Care Unit at Yale and assists in the evaluation of newborn infants with birth defects.

This book has a mere seventy-one pages of text and only three illustrations. These are line drawings by the author, one illustrating all the ossified parts of the skeleton in the full term newborn infant, the second a sort of see-through, half frontal, topographic anatomy of the full-term newborn infant, and the third a mid-sagittal section.

There is no subdivision into chapters or sections, but sequential descriptions of various tissues or organs. The order is based on that of the larger atlas produced by the author a few years ago.

There are some potentially useful statistics in the text, but it is difficult to see of what practical value much of the information can be to the practising paediatrician, pathologist or obstetrician. Thus, the opening section on body weight, size and proportions states that "the average full-term infant (8½ months) weighs about 3,300 gm (7 lb) and the average crown-heel length is about 50 cm (20 inches)", whereas "a premature newborn infant (7 months) weighing only 1,200 gm (3 lb) would have a crown-heel length of about 38 cm (16 inches)". No information is given for any other gestational age. How much more useful would have been a table or graph showing the increase in weight and length with gestation.

Throughout the book there is very little reference to the functional anatomy at various stages of gestation.

Occasional sections do have a few useful details, with some of the implied clinical applications. Thus the development of the lung and its structure is done in some detail and includes comment on surfactant; and the cardiovascular system is also covered in some

detail. In contrast the epidermal ridge pattern of the fingers and palms is dismissed in a single comment that they are unique to the individual, and the section on the brain has practically no comment on its changes during foetal development.

This book is difficult to read as a continuous text, and as a source of reference I think people will prefer the more comprehensive neonatal clinical texts available on various systems.

VICTOR DUBOWITZ

Nutritional Technology

Introduction to Food Science and Technology. By George F. Stewart and Maynard A. Amerine. Pp. xiii+294. (Academic: New York and London, January 1973.) \$12.50.

FOOD science differs from other sciences in drawing on a wider range of disciplines for its techniques; the authors have done well to cover most of them in less than 300 pages. Each chapter is a wide ranging survey of a subject starting with an introduction to the basic concepts and generally succeeding in indicating its scope and depth. The selected references given at the end of each chapter provide a useful introduction to some more detailed sources of information.

The book centres around an excellent chapter "Food processing and preservation" which summarises the diverse techniques used and explains the scientific basis of each. Examples are taken from commercially available products to illustrate these preservation techniques and to explain some of the technological problems encountered with each.

The book starts with a brief history of the development of food processing and then summarises the world food situation, emphasising the important role that food technology will have to play in resolving the world food crisis. There is then a chapter on food quality and its assessment (surprisingly the least successful in my opinion) followed by a survey of human nutrition which includes a section on the effects of raw material handling, processing and storage on the nutritive value of food.

After the chapter on food processing and preservation there are shorter chapters on packaging, safety and sanitation (which includes water supply and effluent treatment), food laws and careers in food science and technology. These last two chapters refer mainly to the United States but still make worthwhile reading for the British student.

Almost all foods are manufactured from natural products and consequently all workers in the field (both scientists and technologists) have to come to

terms with the variability of their raw material. To do this it is essential that they have some knowledge of statistics and agriculture and for this reason I regret that the authors chose not to include a chapter on either subject. Perhaps the inclusion of two further chapters would have increased the cost beyond the means of the "prospective food scientists and technologists" for whom it was written.

The authors must be congratulated on condensing so much of the essence of food science into this book and on maintaining a comprehensible and readable style throughout. It would be a useful addition to the bookshelf of any student of food science as well as to that of graduates of other disciplines starting work in the field.

JOHN WOODMAN

Ethylene in Plants

Ethylene in Plant Biology. By Frederick B. Abeles. Pp. xii+302. (Academic: New York and London, June 1973.) \$18.50.

THERE was a time when auxin was invoked as the master controller of all plant growth and developmental processes. It now seems that ethylene, whose dramatic effects on plants have been known for more than 70 years, is rapidly slipping into that role. In the past 10 years there has been a veritable explosion of research into the physiological actions of ethylene directed towards assessing its significance as a 'natural' hormone.

Dr Abeles has made a thorough survey of the bulky and confusing literature on this topic from the earliest indications of ethylene damage to plants over a century ago to the most recent and sophisticated biochemical and physiological studies. The topics covered are far ranging and include such matters as the practical use of ethylene and related compounds in plant production, the part played by ethylene as an air pollutant, its chemistry and analytical techniques for its estimation. Anybody interested in plant hormones and the chemical control of plant growth and development will find this a mine of information and references.

Having read the book from cover to cover, however, the reader will still be in doubt as to the importance and significance of ethylene as an endogenous growth regulator. Ethylene seems to do everything, but inconsistently, and all this is reported thoroughly and fairly. Although Dr Abeles is clearly a believer in ethylene as a major plant hormone, he has been unable to weave from this tangle of the literature a logical story to convince the sceptic. But he should not be criticised on this score; the time honoured auxin saga is no clearer.

L. J. AUDUS

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CORRESPONDENCE

Smoking in Pregnancy

SIR,—It seems likely that smokers, in general, lead a markedly different life-style from non-smokers, and that the life-style of the smoking mother during pregnancy may be less supportive of the developing foetus. So it is proper to be cautious in interpreting the association between maternal smoking and perinatal death.

In this context, Professor Burch (*Nature*, 245, 277; 1973) notes the evidence, and it is strong, that the low-birth-weight babies of smoking mothers are healthier than those of non-smokers. He seems to suggest that this, too, is evidence against the hypothesis that maternal smoking causes perinatal deaths. Is it not more reasonable to interpret it as merely evidence that maternal smoking is not so harmful to the infant as other causes of low birth weight? In general these causes are very powerfully associated with perinatal death: infants weighing 2,500 g and less at birth are sixteen times more likely to suffer perinatal death than those weighing more than 2,500 g (ref. 1).

Suppose that maternal cigarette smoking causes a weight loss of 5% in each baby: and suppose that each such baby has a 25% greater chance of suffering perinatal death than it would have if the mother had not smoked. Then consider that class of babies weighing less than 2,500 g and born to smoking mothers. About half of them are in that class for no reason other than that, having been born to smokers,

their weight has been reduced, thus transferring them from the heavier class to the lighter one. *Ex hypothesi*, their probability of perinatal death is 25% greater than it would have been if their mother had not smoked. But it is far less than that of the other babies in that class—those who would have been in that class whether their mothers had smoked or not.

In short, the effect of smoking is to augment that class with some relatively healthy babies. So it seems to me that the observed interaction between maternal smoking and birth weight, far from being mysterious, is exactly what would have been expected on the hypothesis that, besides depressing birth weight, maternal smoking has a rather weak causal association with perinatal death.

One would expect a similar interaction between birth weight and any factor if that factor both depressed birth weight and slightly increased the probability of perinatal death.

Let us consider social class, twinning and race. Babies of low social class have higher perinatal mortality rates and lower birth weights than babies in the upper social classes. For weights greater than 3,000 g there is a steady increase in perinatal mortality as social class declines. In the weight class 2,501 to 3,000 g, however, there is a steady decline in mortality rate as social class declines. And in the weight classes less than 2,500 g, there is further evidence that babies born to upper-class mothers are not the healthiest².

Twins have higher perinatal mortality

rates and lower mean birth weights than singletons. However, low-birth-weight twins have a better chance of survival than low-birth-weight singletons³⁻⁶.

In the United States non-white babies have lower mean birth weights and a higher perinatal mortality rate than whites. Nevertheless, among low-birth-weight babies, the non-whites have lower neonatal mortality rates than the whites⁷. In regard to stillbirth rates there is also an interaction (Table 1).

Each of these interactions, viewed in isolation, may be perplexing at first sight. But when seen in conjunction with others, there seems a common-sense explanation behind all of them. I suggest that it applies to maternal cigarette smoking too.

Yours faithfully,

WILLIAM H. JAMES

*The Galton Laboratory,
Department of Human Genetics and
Biometry,
University College London*

¹ Butler, N. R., and Bonham, D. G., *Perinatal Mortality*, 133 (Livingstone, London, 1963).

² Butler, N. R., and Bonham, D. G., *Perinatal Mortality*, 139 (Livingstone, London, 1963).

³ Ferguson, W. F., *Obstet. Gynec., N.Y.*, 23, 861 (1964).

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⁶ Butler, N. R., and Alberman, E. D., *Perinatal Problems*, 133 (Livingstone, London, 1969).

⁷ Shapiro, S., Schlesinger, E. R., and Nesbitt, R. E. L., *Infant and Perinatal Mortality in the U.S.: National Center for Health Statistics, Series 3, 4*, 21 (United States Department of Health, Education and Welfare, Washington, DC, 1965).

⁸ *Vital Statistics of the United States for 1963, Natality*, 1 (United States Department of Health, Education and Welfare, Washington, DC, 1964).

⁹ *ibid.*, *Mortality*, 2, A (1965).

Table 1 Stillbirths (Late Foetal Deaths)/Live Births by Birth Weight and Colour*

	Birth weight (g)								
	1,000 or less	1,001–	1,501–	2,000–	2,501–	3,001–	3,501–	4,001–	4,501–5,000
White	0.655	0.251	0.103	0.030	0.008	0.004	0.003	0.004	0.011
Non-white	0.620	0.264	0.107	0.035	0.010	0.006	0.007	0.013	0.030

* Calculated from official United States data^{8,9}.

Obituary

Professor E. A. Stewardson

PROFESSOR E. A. STEWARDSON, Emeritus Professor of Physics, Leicester University, who died on August 24, 1973, at the age of 68, was born in 1904, and educated at Hawarden County School, North Wales. He graduated from the University of Liverpool in 1924 with first class honours in physics

and took his MSc in 1925. After holding appointments at the University of Liverpool and the National Central University, Chungking, he came to Leicester University College in 1940 and became the first Professor of Physics in 1946. He retired in 1969.

Professor Stewardson's main interest was what nowadays would be called 'atomic physics' rather than 'modern

physics' and a great deal of his research was spent on soft X-ray spectroscopy. Over the years he developed considerable experimental expertise in this field and this was to prove a valuable asset in the latter part of his scientific career.

Professor Stewardson was also a keen amateur astronomer and when, in the late 1950s, it was decided that part of the UK space research programme

should be to investigate the soft X-ray emission of the Sun, it was no surprise that Professor Stewardson's ability was called upon. A collaborative venture between the Universities of Leicester and London ensued, and in 1961 the first direct spectral data for solar soft X-rays were obtained by mounting a soft X-ray spectrometer on a rocket. During the next few years a group devoted to the soft X-ray side of space physics was set up under the direction of Professor Stewardson at the University of Leicester. Some of the successful joint experiments were those on an orbiting solar observatory in 1967 and 1968 and the recently acclaimed X-ray telescope array.

In parallel with the space application of soft X-ray spectroscopy, Professor Stewardson maintained a strong interest in other aspects of atomic physics. He was interested in electron-nuclear collisions and supervised the building and operation of a van de Graaff accelerator in Leicester in the early 1950s.

He will be missed by his colleagues and friends at Leicester.

Announcements

Appointments

THE following have been appointed members and officers of the **International Office of Radiological Protection** for 1973-77. Chairman, **Dr C. G. Stewart** (Canada), **Professor B. Lindell** (Sweden), **Dr D. J. Beninson** (Argentina), **Dr H. Jammet** (France), **Dr J. Liniecki** (Poland), **Dr A. S. McLean** (Great Britain), **Professor Y. I. Moskalev** (USSR), **Dr H. B. Newcombe** (Canada), **Dr E. E. Pochin** (Great Britain), **Professor S.**

Takahashi (Japan), **Professor A. C. Upton** (USA), **Dr J. Vennart** (Great Britain), **Professor Sir Brian Windeyer** (Great Britain). Members Emeritus, **Professor K. Z. Morgan** (USA) and **Dr L. S. Taylor** (USA). Scientific Secretary, **Dr F. D. Sowerby** (Canada).

Professor Francis O'Grady, University of London, has been appointed to the Foundation Chair of Microbiology, University of Nottingham.

The following have been appointed members of the Natural Environment Research Council: **Professor F. G. T. Holliday**, **Professor A. W. Skempton**, **Dr R. G. West**, **Dr I. Maddock**, and **Mr D. J. Lyons**.

Dr K. Hellmann of the Cancer Chemotherapy Unit, Imperial Cancer Research Fund, has been appointed Visiting Professor of Cancer Chemotherapy to the Westminster Medical School, University of London.

Errata

In the bibliography of the book *Notes on the History of Nutrition Research* (reviewed *Nature*, **245**, 442; 1973) the publisher and prices should have read: (Huber: Stuttgart, Berne and Vienna, 1973.) 42 Sw. fr.; 38 DM.

In the article "Model for the Mating Protocol of Synchronously Flashing Fireflies" by J. E. Lloyd (*Nature*, **245**, 268; 1973) paragraph 11, line 7 and following, should read "This is not apparent and perhaps does not occur in most *Pteroptyx* species. I spent many hours within swarms watching individuals and once saw this: a male received a luminescent response to his signals from a female 30 cm away and walked to her and mounted her immediately".

International Meetings

December 3, **The Bragg Lecture** (Dr H. Judith Milledge, Secretary, Bragg Lecture Fund Committee, Chemistry Department, University College London, Gower Street, London WC1).

December 17-21, **Marine Waste Disposal and Marine Pollution** (Istituto di Ingegneria Sanitaria del Politecnico di Milano, Segreteria per i Convegni Internazionali, Piazza Leonardo da Vinci 32, 20133 Milan).

December 18, **Second Scottish Perkin Symposium** (Professor P. L. Parson, Department of Pure and Applied Chemistry, University of Strathclyde, Cathedral Street, Glasgow G1 1XL).

December 18-19, **545th Biochemical Society Meeting** (Meetings Officer, The Biochemical Society, 7, Warwick Court, Holborn, London WC1R 5DP).

Reports and Publications

not included in the *Monthly Books Supplement*
Great Britain and Ireland

Clean Air Council. Working Party on the Publication of Information about Industrial Emissions to Atmosphere. Pp. 29. (London: Department of the Environment (Room 541), 28 Broadway, SW1, 1973.) [107]

Agricultural Research Council. Letcombe Laboratory—Annual Report for 1972. Pp. ix+69. (London: Agricultural Research Council, 1973. Obtainable from HMSO.) 85p. [107]

University of Oxford. Annual Report of the Curators of the Bodleian Library for 1971/1972. Pp. 61. (Supplement No. 6 to the *University Gazette*, Vol. CIII, June 1973.) (London: The University, 1973.) £1. [107]

Energy World, No. 1, July 1973. (Bulletin of the Institute of Fuel.) Pp. 1-32. (London: The Institute of Fuel, 1973.) [107]

Element Cards: a Games Approach to Mastery of the Chemical Elements. By Joseph Lipson. £2.40; DM 20. Teacher's Guide. Pp. 96. £1.25; DM 10.50. (London: Heyden and Son, Ltd.; Rheine/Westf.: Heyden and Son, GmbH, 1973.) [107]

The Zoological Record. 1968, Vol. 105, Section 20: List of New Generic and Subgeneric Names Recorded in Volume 105. Compiled by H. O. Ricketts. Pp. 18. 1969, Vol. 106, Section 13: Insecta. Compiled by the Staff of the Zoological Society of London. Pp. xii+589. £12; \$29. (London: The Zoological Society of London, 1973.) [107]

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